Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review and Meta-analysis

Comparison of COVID-19 outcomes in patients with Type 1 and Type 2 diabetes: A systematic review and meta-analysis

Arman Shafiee [a, b, *], Mohammad Mobin Teymouri Athar [c], Mahmoud Nassar [d], Niloofar Seighali [b], Dlnya Aminzade [c], Payam Fattahi [c], Maryam Rahmannia [c], Zahra Ahmadi [e]

[a] School of Medicine, Alborz University of Medical Sciences, Karaj, Iran
[b] Student Research Committee, Alborz University of Medical Sciences, Karaj, Iran
[c] School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[d] Medicine Department, Icahn School of Medicine at Mount Sinai / NYC Health + Hospitals / Queens, New York, USA
[e] Department of Basic Sciences and New Technologies, Electronical Branch, Islamic Azad University, Tehran, Iran

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ABSTRACT

Background and aims: This systematic review and meta-analysis aimed to evaluate the current evidence available to investigate clinical outcomes between patients with type 1 and type 2 diabetes.
Methods: MEDLINE (Pubmed), Scopus, Web of Science, Cochrane library, Google scholar and Clinicaltrials.gov were searched. Randomized controlled trials (RCTs), non-randomized trials, and observational studies were eligible for inclusion. National Institutes of Health Quality Assessment Tool was used to assess the quality. Data were pooled by the Restricted-maximum-likelihood random-effects approach.
Results: Total 11 studies comprising 7690415 individuals were included in this study. The log OR for the pooled data for all-cause mortality rate was −0.71 (95% CI: −1.38 to −0.03). Based on the pooled results, type 1 diabetic COVID-19 patients may have a better prognosis for mortality. There were no significant differences between groups in term of ICU-admission log OR -0.22 (95% CI: −0.81 to 0.37), and hospitalization log OR -0.48 (95% CI: −1.23 to 0.27). Based on our descriptives analyses after adjusting for age and comorbidities, the high-risk group in three studies was type 2 diabetes, and in five studies was type 1. Two studies reported no significant difference between these groups in relevant outcomes.
Conclusion: There were no significant differences in disease severity between type 1 and type 2 diabetes. Based on the unadjusted data available, the mortality rate for people with type 1 diabetes was shown to be lower than that for people with type 2. As data on these subjects is scarce, and the results obtained from studies are heterogeneous, further research with adequate sample sizes is needed to precisely compare the outcomes of COVID-19 between type 1 and type 2 diabetes.

1. Introduction

World Health Organization (WHO) declared novel Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) a pandemic for March 11, 2020 [1]. As a result, its high transmissibility has caused more than 6 million deaths worldwide, and the number continues to increase as new strains emerge [2]. Symptoms of the disease may range from asymptomatic or mild to severe pneumonia, multi-organ failure, acute respiratory distress syndrome (ARDS), and even death [3,4]. Comorbidities are one of many risk factors contributing to the severity of the disease [5]. Studies have established a significant relationship between the risk of mortality in COVID-19 patients and certain comorbidities, including chronic kidney disease (CKD), chronic lung disease, diabetes mellitus (DM), hypertension, aging, immunosuppression, and obesity [6]. An analysis by the Chinese CDC of 72314 patients indicates that diabetes is the second most common cause of death (7,3%) after heart disease (10,5%), which equates to a rate of 2,3% in the general population [7].

Diabetes mellitus (DM) is a chronic disease characterized by glucose dysregulation and severe long-term complications affecting multiple organs. Type 1 diabetes (T1D) and type 2

* Corresponding author. School of Medicine, Alborz University of Medical Sciences, Karaj, Iran.
E-mail address: armanshafieemd@gmail.com (A. Shafiee).

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diabetes (T2D) are the most prevalent subtypes of diabetes. Nearly half a billion people suffer from DM, making it one of the most important risks for severe COVID-19. Moreover, DM is often associated with other risk factors, including hypertension, nephropathy, obesity, cardiovascular disease (CVD), a proinflammatory and hypercoagulable state that makes the individual more susceptible to hyperglycemia and more severe forms of COVID-19 [8–11]. The prevalence of T1D ranged from 0.15% to 28.98% among COVID-19 patients [12]. The risk of progression to severe COVID-19 and death is more significant in patients with diabetes mellitus (DM) [13]. As a result of the impairment of the immune system caused by DM, an uncontrolled immune response was produced against SARS-CoV-2 [14]. Bidirectional interrelationships between SARS-CoV-2 and DM complications will result in a more complex situation in terms of disease severity.

Due to the high prevalence of diabetes among COVID-19 patients and the special care that is needed during infection, we are concerned about preventing and treating COVID-19 in patients with diabetes. A number of studies have reported an association between diabetes and a higher risk of severe COVID-19; however, it is unclear which types of diabetes are associated with a higher risk of severe disease progression. In order to fill this evidence gap, we conducted a systematic review and meta-analysis to compare T1D and T2D in terms of disease severity.

2. Methods

2.1. Search strategy

We conducted a systematic review and meta-analysis in accordance with the recommendations of the Cochrane Handbook [15]. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in this study [16]. Our study protocol is registered at PROSPERO under the number CRD42022319173.

Pubmed/MEDLINE, Scopus, Web of Science, Cochrane library, and Clinicaltrials.gov were assessed by our reviewers (N.S and D.A and M.R and Z.A) who designed a search strategy using the search string: ("COVID-19" [Mesh]) OR ("SARS-CoV-2" [Mesh]) OR "COVID-19″ OR "Coronavirus" OR "nCoV" OR "SARS-Cov-2″ AND ("Diabetes " [Mesh]) OR "Diabetes" OR "diabetes mellitus" OR "diabetes mellitus type 1″ OR "diabetes mellitus type 2″ OR "diabetes type 1″ OR "diabetes type 2". All publications were retrieved up to February 16, 2022. Additionally, we searched the reference sections of other studies for relevant publications. The result was exported to the EndNote X9 program for further screening.

2.2. Study selection and data extraction

Studies recognized as eligible for inclusion included: 1) confirmed COVID-19 patients; 2) patients diagnosed with T1D and T2D; 3) studies evaluating outcomes relevant to this topic; and 4) studies reporting both T1D and T2D infected with SARS-CoV-2. We included randomized controlled trials (RCTs), non-randomized trials, and observational studies. We excluded case reports, case series, non-English articles, and studies that involved patients <18 years old and pregnant women. Additionally, studies that focused on only one type of diabetes (for instance, studies focused exclusively on T2D) were excluded. Two reviewers independently reviewed the titles and abstracts (N.S and D.A), then the full texts in EndNote. All disagreements were resolved via discussion with a third reviewer to reach an agreement (AS). Data were extracted from text, tables, figures, graphs, and supplementary materials into an excel spreadsheet. Two reviewers (N.S. and A.S.) independently extracted author/year, country, study type, population, duration, number of patients in each trial, as well as outcome data.

2.3. Quality assessment

Two reviewers (M.T and A.S) independently evaluated the included studies using the NIH risk of bias checklist [17]. The checklist included 14 questions designed to assess the quality of observational cohort and cross-sectional studies. The studies with 10 or more yeses are rated as "Good", 7–9 yeses as "Fair", and fewer than 7 yeses are rated as "Poor".

2.4. Outcome measure

The meta-analysis outcomes were all cause mortality, hospitalization, and ICU admission rates for COVID-19 patients with T1D compared to COVID-19 patients with T2D.

2.5. Data synthesis and analysis

In this study, data were pooled by the Restricted-maximum-likelihood random-effects approach since the indicators were designed to vary across studies, and there was some variation between the studies. A log odds ratio (log OR) was calculated to summarize the overall effects of outcomes. A p-value of <0.05 was considered significant for the effect estimate. The I^2 statistic was used to assess study heterogeneity, with I2 values of <50%, 50%–75%, and >75%, respectively, indicating low, moderate, and high levels of heterogeneity. Although I^2 is the most commonly used measure of heterogeneity, the I^2 value increases as the number of trials increases. This makes it challenging to compare I^2 across analyses. Therefore, we report both I^2 and Tau for each analysis. Publication bias was assessed using funnel plots inspection and Egger's regression test for funnel plot asymmetry. To evaluate the effect of individual studies on the pooled results, we conducted a leave-one-out sensitivity analysis. A sub-group analysis was conducted for both the adjusted and unadjusted data. We used Stata version 16 statistical software (Stata Corp, College Station, TX, USA) for the quantitative synthesis.

3. Results

A total of 2419 initial studies were identified, and 638 duplicates were removed (Fig. 1). After screening the titles and abstracts, 39 full-text articles were reviewed, and 11 studies were included.

3.1. Characteristics and quality of included studies

Most of the studies were conducted in European countries, including Austria (n = 1), Sweden (n = 1), Scotland (n = 1), France (n = 1), England (n = 4), and Turkey (n = 1). Two studies were conducted in the United States (n = 2). The studies considered were all observational, and eight of them had a sample size of more than 1000 patients. Detailed characteristics of each study is provided in Table 1. On the basis of the NIH checklist, the quality of included studies was evaluated as Good/Fair and none was rated Poor. Most of the studies did not provide additional information about blinding outcome assessors to the participants' exposure status or assessing the exposure in more than one study.

3.2. Mortality

A total of eight studies, including 7379184 COVID-19 patients with T1D or T2D, reported a mortality rate in their studies (Fig. 2-A) [18–25]. Log OR for the pooled data was −0.71 (95% CI: −1.38 to −0.03) with high heterogeneity (I^2 = 98%, Tau = 0.67). Based on the pooled results, T1D COVID-19 patients may have a better prognosis for mortality. Our analysis of subgroups using adjusted/

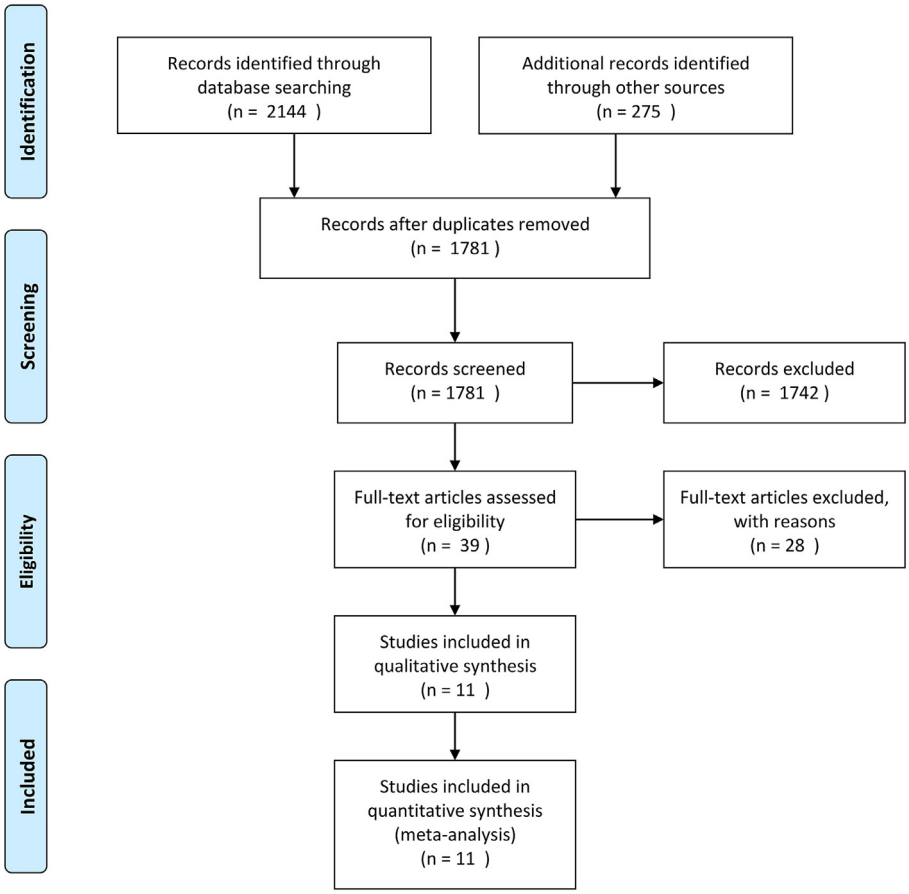


Fig. 1). Database search and selection based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) approach.

unadjusted data revealed a pooled log OR of −0.95 (95% CI: −1.41 to −0.48) for unadjusted data and 0.83 (95% CI: 0.41 to 1.25) for adjusted data (Fig. 3-A). According to the sensitivity analysis performed using the leave-one-out method, the overall effect would be substantially altered if any study were excluded (except for the study by Demirci et al. [26] (Fig. 4-A). Upon examination of funnel plots and Egger's regression test (p = 0.43), there was no evidence of publication bias (Fig. 5-A).

3.3. ICU admission

There have been six studies reporting rates of hospitalization for T1D or T2D, including 1422426 patients with COVID-19 (Fig. 2-B) [19,20,22–24,27]. Pooled log OR was −0.22 (95% CI: −0.81 to 0.37) with high heterogeneity (I^2 = 88%, Tau = 0.39). The pooled results indicate that there was no difference between T1D and T2D in patients with COVID-19. Based on subgroup analyses of adjusted/unadjusted data, we found a pooled log OR of −0.52 (95% CI: −0.97 to −0.06, I^2 = 72%) for unadjusted and 0.60 (95% CI: 0.20 to 0.99) for adjusted data (Fig. 3-B). A sensitivity analysis using the leave-one-out method showed that the overall effect was substantially altered when the study by Demirci et al., was omitted [26] (Fig. 4-B). According to the funnel plot and Egger's regression test (p = 0.33), there is no publication bias (Fig. 5-B).

3.4. Hospitalization

A total of six studies, including 1112951 COVID-19 patients with T1D and T2D, reported hospitalization rates (Fig. 2-C) [19,22–24,28,29]. We calculated the pooled log OR to be −0.48 (95% CI: −1.23 to 0.27) with high heterogeneity (I^2 = 97%, Tau = 0.78) between the groups. It was found that there was no difference between COVID-19 patients with T1D and T2D. Subgroup analysis based on adjusted and unadjusted data shows a pooled log OR of −0.93 (95% CI: −1.65 to −0.21, I^2 = 96%) for unadjusted data and 0.43 (95% CI: −0.01 to 0.87) for adjusted data (Fig. 3-C). When the leave-one-out method was used, the overall effect was not substantially altered when any single study was omitted (Fig. 4-C). Upon examination of the funnel plot and Egger's regression test (p = 0.0533), there was no evidence of publication bias (Fig. 5-C).

3.5. Descriptive synthesis for outcomes after adjustment

The majority of the studies included in our quantitative synthesis that provided the necessary information for our synthesis were data from registries without any adjustment for age or other comorbidities between T1D and T2D patients with COVID-19 disease. In their own studies, however, they have reported their results after further adjustment as well as their unadjusted results. As a result of adjusting for age and comorbidities, the high-risk group in three studies was T2D, five studies were T1D, and two studies reported no significant difference between these groups in relevant outcomes.

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis comparing the severity of COVID-19 between

Table 1
Summary characteristics of included studies.

Author/Year	Country	Type of study	Duration	Population	Total patients	Age	T1D Total	T1D Age	T1D Co-morbidity	T2D Total	T2D Age	T2D Co-morbidity	Final results	Quality
Sourij [18],/ 2020	Austria	Combined prospective and retrospective multicenter cohort study	From April to June 2020	Hospitalized people aged 18 years or older with a confirmed positive throat swab for SARS-CoV-2 and a confirmed diagnosis of type 1 diabetes, type 2 diabetes or prediabetes	238	71.1 ± 12.9	11	N.A.	N.A.	180	N.A.	N.A.	No significant differences for mortality between people with T1D and T2D.	Fair
Rawshani, [19]./2021	Sweden	Retrospective case control cohort study	Till January 1, 2020	Adult patients (>18) with type 1 and type 2 diabetes with at least one registration in the NDR between January 1, 1998 and January 1, 2020, and who were alive on Jan 1, 2020	456,615	N.A.	44639	42.60 ± 16.56	Coronary heart disease: 3490 Acute myocardial infarction: 1736/ Stroke: 1357 Heart failure: 1474 Valvular disease: 528/ Atrial fibrillation: 1212/Hypertension: 15474 Peripheral arterial disease: 1518 Chronic obstructive pulmonary disease: 489/Dementia: 243/ Asthma: 2965 Alcoholism: 2651 Substance abuse: 3726/Schizophrenia: 399/Renal disease: 5470/Cancer: 2701	411976	66.05 ± 13.24	Coronary heart disease: 85814 Acute myocardial infarction: 42581/ Stroke: 35793 Heart failure: 44215 Valvular disease: 15278/Atrial fibrillation:56522/ Hypertension: 228441 Peripheral arterial disease: 15904 Chronic obstructive pulmonary disease: 21210/Dementia: 10834/Asthma: 26936 Alcoholism: 16785 Substance abuse: 29018/Schizophrenia: 8963/Renal disease: 35382/Cancer: 81715	Increased risk for T2D after adjustment, T1D did not show an excess risk for outcomes after adjustment; reassuringly for this group, there were very few deaths and admissions into intensive care.	Good
McGurnaghan, [27]./2021	Scotland	Cohort study	From March to July 2020	Total population of Scotland, including all people with diabetes who were alive 3 weeks before the start of the pandemic in Scotland (estimated Feb 7, 2020)	5,463,300	66·7	34 383	44.5 (29.7,58.3)	Any heart disease: 4847, Asthma or chronic lower airway disease: 8704, Neurological and dementia (excluding epilepsy): 1390, Liver disease: 160, Immune disease or on immunosuppressants: 629,	275 960	68.4 (59.1,76.9)	Any heart disease: 93891, Asthma or chronic lower airway disease: 93704, Neurological and dementia (excluding epilepsy): 13460, Liver disease: 2698, Immune disease or on immunosuppressants: 3161	Adjusted odds ratio of patients with fatal or critical care unit-treated COVID-19 in T1D was higher comparing T2D.	Good
Lasbleiz (28)./ 2020	France	Retrospective monocentric observational cohort study	From March to April 2020	COVID-19 diagnosis confirmed biologically (by SARS-CoV-2 PCR test) and/or radiologically (ground-glass opacity and/or crazy paving on chest computed	344	62.1 ± 14.0	20	40.1 ± 15	N.A.	324	63.5 ± 13	N.A.	Most of T1D patients were managed as out-patients. After adjustment, patients with T2D always had a much greater risk of being hospitalized than T1D.	Good

				tomography scan) and a personal history of diabetes or newly diagnosed diabetes on admission (glycosylated hemoglobin HbA1c $\geq$ 6.5% during hospitalization)										
Kempegowda [20],/2021	England	Retrospective cohort study	From March to May 2020	All patients treated for DKA between March 1, 2020 and May 30, 2020	88	59.8	5	30.9	N.A.	15	63	N.A.	T2D were more likely to need ICU with higher mortality rates comparing T1D.	Fair
Holman [21]./ 2020	England	Population-based cohort study	Till May 11, 2020.	People with diagnosed diabetes who were registered with a general practice	3138410	N.A.	264 390	46·6 (SD 19·6)	Previous myocardial infarction: 3095/ Previous stroke: 3160/ Previous heart failure: 6825/Any cardiovascular or renal morbidity: 31 790/a recent history of one or more prescriptions for antihypertensive drugs: 115 660	2 874 020	67·5 (SD 13·4)	Previous myocardial infarction: 48 340/ Previous stroke: 57 095/Previous heart failure: 138 045/Any cardiovascular or renal morbidity: 624 995/ 2 185 920	People with an HbA1c of 86 mmol/mol or higher had increased COVID-19-related mortality (hazard ratio 2.23 in T1D and 1.61 in T2D)	Good
Gregory [22]/ 2021	United States	Prospective cohort study	From March to August 2020	Case subjects with COVID-19 across a regional health care network of 137 service locations	6451	N.A.	40	37/table2 with 37 patients: 32	hypertension:13/ asthma: 2/Taking any antihypertensive medication: 25	273	58	hypertension:194/ asthma: 28/Taking any antihypertensive medication:269	After adjustment, both groups with diabetes (T1D and T2D) had similar odds of worsening morbidity.	Good
Gao [23]./2021	England	Prospective, community-based, cohort study	From January to April 2020	Individuals aged 20 −99 years who were registered at a general practice (GP) that contributes to the QResearch database and had available BMI data	6910695	N.A.	44 248	N.A.	N.A.	577 246	N.A.	N.A.	N.A.	Good
Demirci [26]/ 2022	Turkey	Nationwide retrospective cohort	From March to May 2020	Patients with confirmed (PCR positive) COVID-19 infection between 11 March through May 30, 2020	149,671	N.A.	163	41	Smoking: 29/ Hypertension: 110/ Dyslipidaemia: 80/ Obesity: 5/ Asthma,COPD: 57/ Chronic kidney disease:43/Coronary artery disease (CAD):65/Cancer: 8/ Microvascular complications: 77/ Macrovascular complications:73/ Taking RAS blocker: 78	33,478	54	Smoking: 3612/ Hypertension: 22897/ Dyslipidaemia: 14923/ Obesity:2112/Asthma, COPD: 2112/Chronic kidney disease:2187/ Coronary artery disease (CAD):10778/ Cancer: 2402/ Microvascular complications: 6120/ Macrovascular complications:11864/ Taking RAS blocker: 15746	Patients with T1D had worse prognosis of COVID-19 compared to T2D patients.	Fair

(*continued on next page*)

Table 1 (*continued*)

Author/Year	Country	Type of study	Duration	Population	Total patients	Age	T1D Total	T1D Age	T1D Co-morbidity	T2D Total	T2D Age	T2D Co-morbidity	Final results	Quality
Kompaniyets [29],/2021	United States	Cohort	From March 2020 through January 2021	COVID-19 patients aged 18 years and younger	43465	12 [4–16]	255	12 to 18	N.A.	289	12 to 18	N.A.	T1D was among the strongest risk factors for severe COVID-19 in patients aged 18 years or younger. Adjusted risk ratio showed excess risk for T1D compared to T2D patients.	Good
Barron [25],/2020	England	Cohort	From March to May 2020	All COVID-19 individuals registered with a general practice in England	61414470	40×9 ± 23×2	263830	46.6 ± 19.5	Coronary heart disease:25375, Cerebrovascular disease:9680, Heart failure:8485	2864670	67.4 ± 13.4	Coronary heart disease:550475, Cerebrovascular disease:190410, Heart failure:178210	Greater increased odds in people with T1D than in people with T2D.	Good

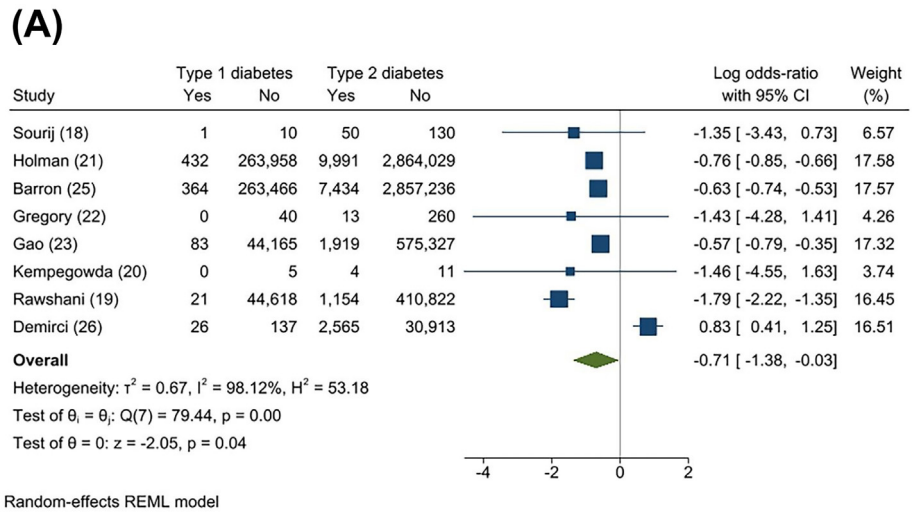
Abbreviations: T1D: Type 1 diabetes, **T2D:** Type 2 diabetes, **NDR:** The National Diabetes Registry, **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2, **N.A.:** Not Applicable, **PCR:** Polymerase Chain Reaction, **DKA:** Diabetic ketoacidosis, **ICU:** Intensive Care Unit, **BMI:** Body Mass Index, **COVID-19:** Coronavirus Disease-2019, **RAS:** Renin–Angiotensin System, **GP:** General Practice, **CAD:** Coronary Artery Disease.

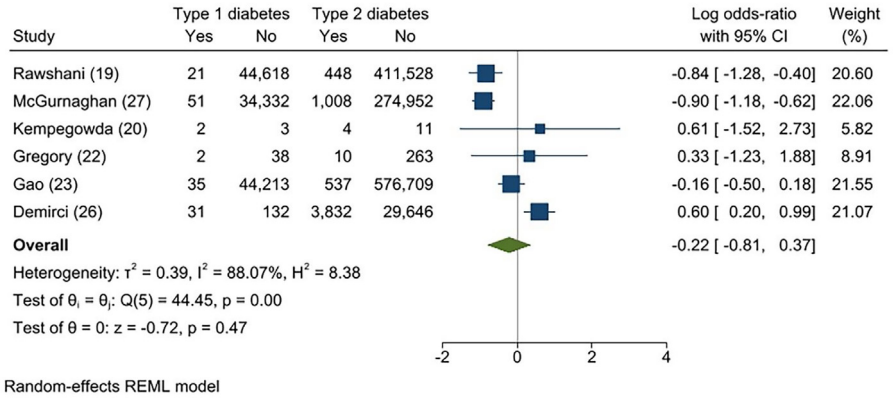
patients with T1D and T2D. This review included 11 studies with a total of 77583747 patients with concurrent SARS-CoV-2 infection and diabetes. This study examined the clinical outcomes of patients with diabetes to determine if there were any differences between the two groups of patients. Our clinical outcomes representing the severity of the disease included hospitalization, ICU admission, and mortality. As a result of our analyses, patients with T1D had a better outcome, although the difference was not statistically significant when comparing ICU admission and hospitalization rates. Furthermore, it should be noted that most of these results were obtained from unadjusted data collected from included studies, which did not take into consideration age and other comorbid conditions in these patients. Our descriptive synthesis considering the impact of other factors revealed an interesting result. Based on the majority of included studies, T1D patients were at a higher risk for COVID-19 after adjusting for age and other comorbidities.

Various reports from around the world indicate that the prevalence of diabetes among hospitalized COVID-19 patients can reach as high as 20% [30]. Further, epidemiological studies suggest that diabetes is more prevalent among individuals with severe disease and is associated with a higher mortality rate [31]. Furthermore, patients with diabetes are more likely to acquire infections such as lower respiratory tract infections due to impaired immune function, including a lack of proper phagocytosis by neutrophils, macrophages, and monocytes [32]. Hyperglycemia is also associated with an increased risk of severe infections [33]. Therefore, patients with diabetes are at greater risk of developing more severe forms of the disease and even death. Together, these factors result in higher COVID-19 morbidity and mortality, placing a great burden on healthcare systems and other aspects of people's lives. Considering public health perspectives, with the emergence of new variants and their rapid spread, the number of patients admitted to hospitals, especially intensive care units, has grown dramatically. As such, it is crucial to establish protocols that prioritize patients based on their estimated risk of severe disease and death. Special attention should be paid to patients with conditions associated with more severe outcomes, such as older age, diabetes, hypertension and obesity, as they are more likely to suffer complications. As a result of this condition, COVID-19 can be prevented through improved social distancing and personal protective equipment, enhanced patient vigilance, and a lower threshold for testing, hospitalization, and intensive care for patients with diabetes.

Both T1D and T2D are the most prevalent types of diabetes mellitus. Although both groups are at risk of severe outcomes, there are differences between them as two pathophysiologically distinct conditions. In COVID-19 patients with both types of diabetes, the mortality rate is associated with age, male gender, cardiovascular disease (CVD), renal impairment, obesity, and underweight [34]. BMI could be a determining factor when comparing these two subtypes since it is more prevalent among patients with T2D. According to Trieu et al., elevated BMI is evident among patients with T2D when these two subtypes are compared [35]. During the pandemic, various factors, including lockdown, sedentary lifestyle, decreased physical activity, and increased calorie intake contributed to increased population body mass index. According to the CDC, the BMI increased twofold during the pandemic compared to the period before the pandemic [35].

As Rawshani et al. reported, there is an independent association between T2D and risk of hospitalization, admission to ICU, and mortality [34]. They noted that the risk remains, but it was reduced after adjusting for confounding factors. Despite adjusting for confounding factors, there was no independent risk of these outcomes in T1D patients. Ultimately, the researchers concluded that long-term complications of the disease influenced the risk in patients with T1D. In addition, the researchers found that women had a





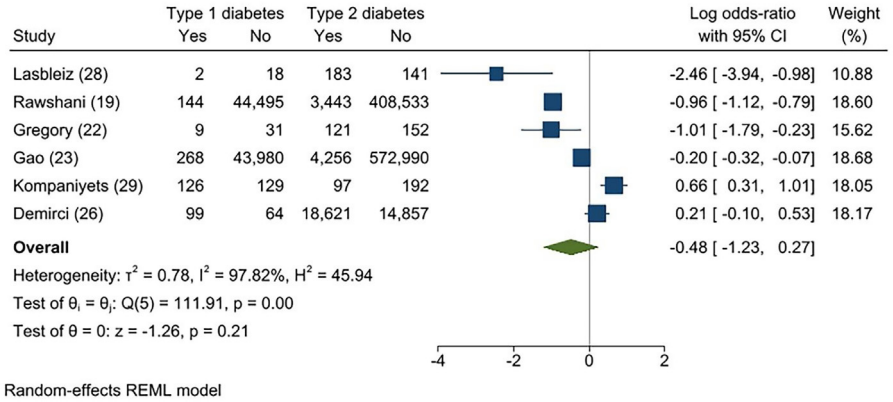


Fig. 2). Forest plots showing the results of meta-analyses for comparing COVID-19 outcomes in patients with type 1 and type 2 Diabetes. A) The rate of mortality was significantly lower in patients with type 1 diabetes, B) No significant difference was observed in terms of ICU admission between type 1 and type 2 diabetes, C) No significant difference was observed in terms of hospitalization between type 1 and type 2 diabetes,.

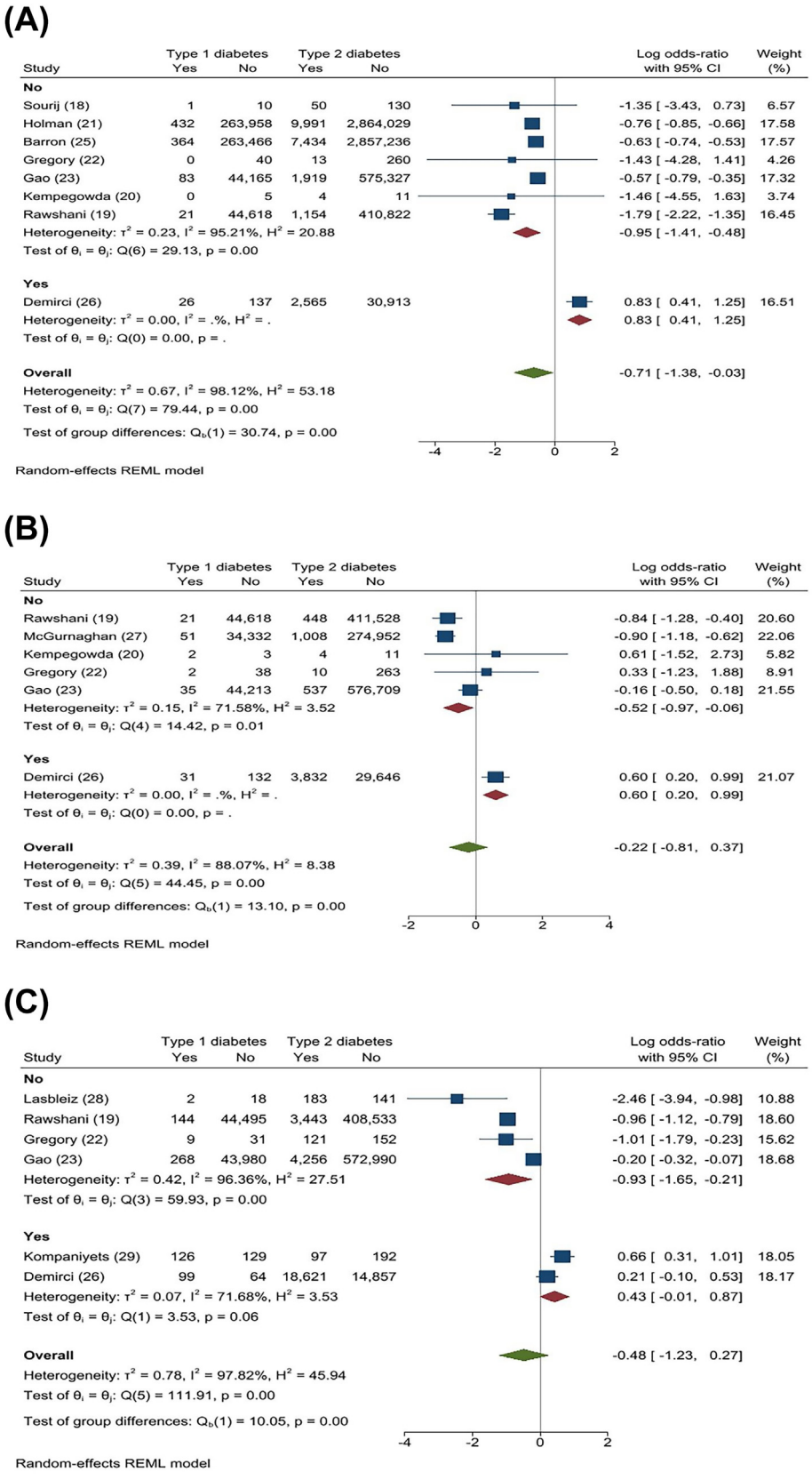


Fig. 3). Sub-group meta-analysis based on adjusted/unadjusted data available for age, sex, and comorbidities. Most of the included studies only reported OR/RR after adjustment, therefore, large amount of data in meta-analysis are unadjusted for possible confounders. A) Mortality, B) ICU admission, C) Hospitalization. Yes: adjusted data; No: unadjusted data.

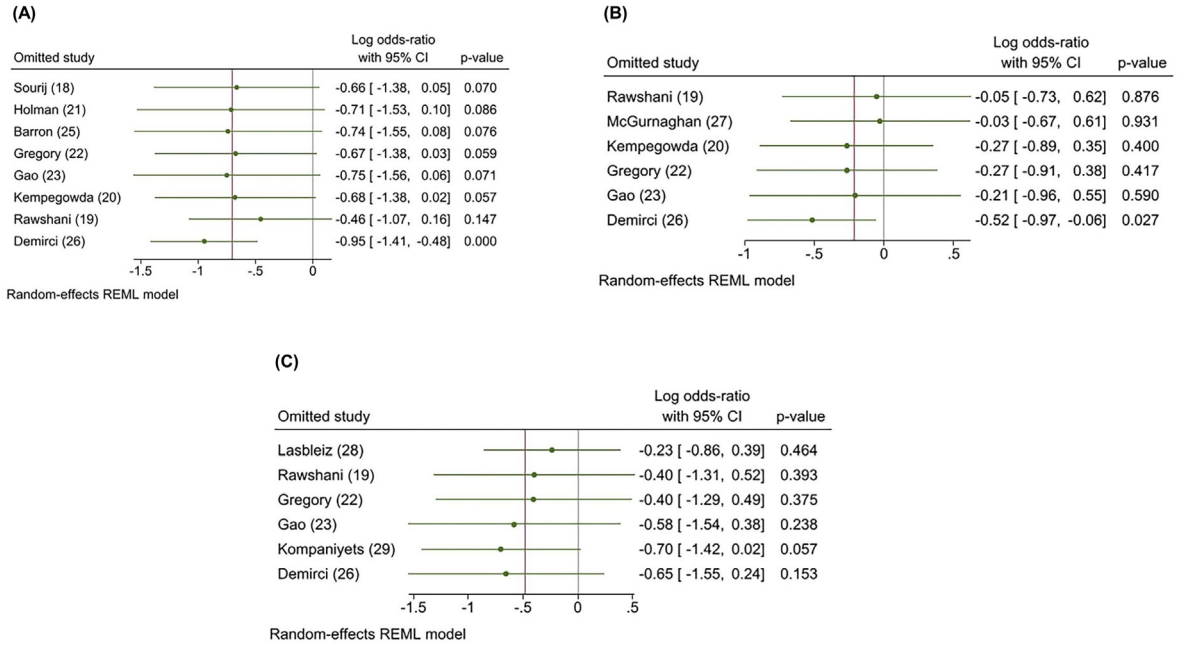


Fig. 4). Sensitivity analyses of outcomes based on leave-one-out method. A) Mortality, B) ICU admission, C) Hospitalization.

lower risk for these outcomes among patients with T2D, whereas the risk was the same for patients with T1D [34].

According to the English national audit cohort, compared to individuals without diabetes, the odds ratios for COVID-19 deaths in the hospital were 3.51 in T1D patients and 2.03 in T2D patients [28]. Due to limitations associated with the datasets used in the study, confounding factors such as hypertension, CKD, BMI, and smoking status were not adjusted [25]. A matched case-control study from Scotland reported ORs of 2.75 and 1.60 for T1D and T2D, respectively [27]. Lasbleiz et al. reported a much higher hospitalization risk for T2D patients after adjusting for age and BMI, whereas T1D patients may be reassured [28].

In Gregory et al. 's study, the odds of hospitalization and more severe disease were similar between T1D patients and T2D patients [22]. According to Demirci et al., a nationwide cohort study was conducted with 149,671 patients who tested positive for COVID-19 [26]. They found that despite adjusting for age, gender, and microvascular and macrovascular complications, patients with T1D had a threefold greater risk of ICU admission and mortality than people with T2D. They described the scarcity of data regarding T1D due to the low prevalence of T1DM, the younger age of T1DM patients compared to T2DM patients, and the fact that elders are at a greater risk of becoming affected by COVID-19. They concluded that these two subtypes of diabetes mellitus are entirely different in their clinical outcomes based on their findings. In addition, the different immune dysfunction and pathophysiology may be contributing to the higher mortality rate associated with T1D [26]. COVID-19 mortality has an inverse relationship with eGFR [30]. As eGFR values may change after taking anti-diabetic medications, there is concern that the use of these drugs may impact mortality rates.

5. Strengths and clinical relevance

Our study has several strengths. This is the first systematic review and meta-analysis to examine COVID-19 severity differences between T1D and T2D. We conducted a comprehensive database search in order to obtain the most comprehensive results and accurate conclusions. The analysis of each outcome was also based on at least five studies. Additionally, most of the studies included measured and differentiated the level of baseline characteristics that may vary in amount or level, such as HbA1c. These findings may have implications for clinical practice and public health policies. While chronic hyperglycemia is the primary cause of diabetes

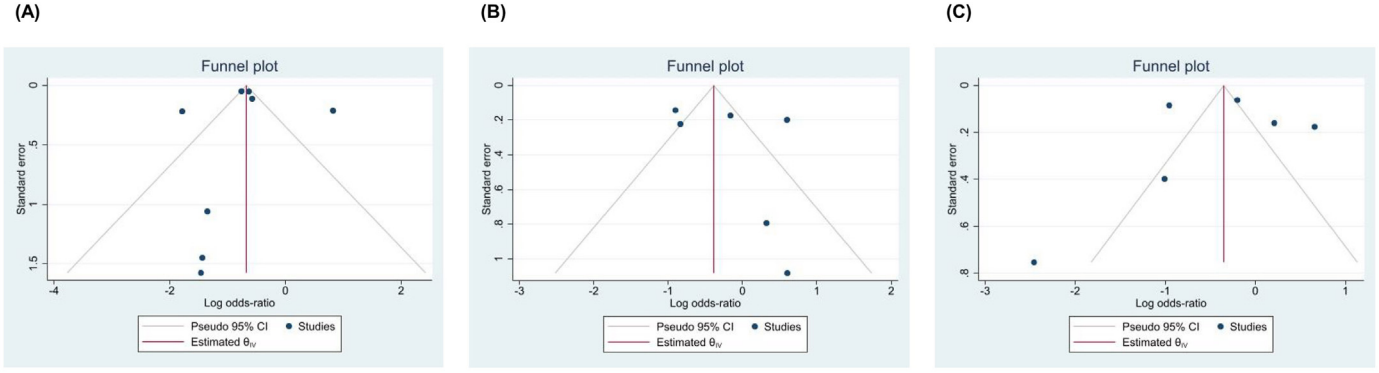


Fig. 5). Funnel plot of outcomes for evaluation of publication bias. A) Mortality, B) ICU admission, C) Hospitalization.

mellitus, type 1 and type 2 diabetes differ in terms of their pathophysiology, preventive methods, age of onset, management, and epidemiological characteristics. As a result, the approaches needed to treat these two types of diabetes differ. It is beneficial for us to identify which type of diabetes leads to more severe forms of COVID-19 in order to determine the preventive measures needed to reduce the number of affected individuals and further complications associated with concurrent COVID-19 infection. Specifically tailored education and management can be provided to patients with each type of diabetes to achieve this objective.

The fact that T2D is more prevalent and develops at an older age than T1D indicates that the disease severity in patients with these two types of diabetes warrants special consideration for prevention and management. Furthermore, management of T1D is based on insulin therapy. On the other hand, the management of T2D includes a variety of anti-diabetic medications, which may cause different side effects, increasing the risk of alterations to the health status of patients. Diabetic ketoacidosis (DKA) is a severe acute metabolic condition characterized by acidosis, ketosis, and hyperglycemia that occurs more frequently among patients with type 1 diabetes [36]. It is important to assess the risk of severe disease for patients who are more vulnerable to DKA as this is a life-threatening condition. We found that both types of patients have the same risk of developing severe disease; therefore, there is no need to prioritize these two patient types when it comes to providing health care services.

6. Limitations

As our study was subject to several limitations, its results should be interpreted with caution. Most of the analyzed studies were cohort studies, so they may be prone to bias related to their retrospective nature. The populations of the included studies were clinically heterogeneous. For example, one study included pediatric patients, while others included adult patients. In addition, some studies included very few participants, whereas others were national studies including large numbers of participants. The timing of the studies and the region in which they were conducted may have affected the results, as there were a number of differences between included studies. Furthermore, the heterogeneity of the results obtained from the studies is high; however, meta-analyses based on observational studies are often highly heterogeneous [37]. Lastly, it should be noted that most of our quantitative synthesis includes unadjusted data for age, gender, and other comorbidities due to the fact that confounding factors such as elderly age, cardiovascular disease, hypertension, and obesity are associated with severe COVID-19 and increased mortality.

We conclude, based on our results, that there are no significant differences between T1D and T2D in terms of severity of the disease. The mortality rate for people with T1D was observed to be lower than that for people with T2D based on the unadjusted data available. As data on these subjects is scarce, and the results obtained from studies are heterogeneous, further research with adequate sample sizes is needed to precisely compare the outcomes of COVID-19 between T1D and T2D.

Author contributions

Arman Shafiee: Conceptualization, Investigation, Project administration, Writing- original draft, Writing-review & editing.

Mohammad Mobin Teymouri Athar, Mahmoud Nassar: Investigation, Writing- original draft, Writing-review & editing.

Niloofar Seighali, Dlnya Aminzade, Payam Fattahi, Maryam Rahmannia, and Zahra Ahmadi: Conceptualization, Investigation, Writing- original draft.

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Ethics approval

Not applicable.

Data availability

Data sharing is available by contacting corresponding author.

Declaration of competing interest

No Conflict of interest.

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