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SYSTEMATIC REVIEW

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# Type 2 diabetes mellitus as a predictor of severe outcomes in COVID-19 — a systematic review and meta-analyses

Babatunde Fatoke[1,2], Amrit Lal Hui[3], Muhammad Saqib[4], Mrinal Vashisth[3], Stephen Olaide Aremu[2,5*], Dorcas Oluwakemi Aremu[6] and Deborah Bukola Aremu[7]

## Abstract

**Background** The COVID-19 pandemic has posed significant challenges to global health, with type 2 diabetes mellitus (T2DM) emerging as a key risk factor for adverse outcomes. This study systematically reviews and quantifies the association between T2DM and COVID-19 outcomes, including mortality, severity, and need for mechanical ventilation.

**Methods** A systematic review and meta-analysis were conducted that adhered to PRISMA guidelines. We searched PubMed, Scopus, Web of Science and Embase for studies published from december 2019 to march 2024. Eligible studies reported on the impact of T2DM on COVID-19 outcomes in the adult population. Data were extracted and analyzed using a random-effects model, and heterogeneity was assessed using the $I^2$ statistic. Publication bias was assessed using Egger regression, Kendall's Tau, and the Fail-safe N calculation.

**Results** Eighteen studies were included in the meta-analysis for mortality, six for severity and five for mechanical ventilation. T2DM was significantly associated with higher mortality (OR = 3.66, 95% CI: 2.20–5.11, $p < 0.001$), higher severity (OR = 1.97, 95% CI: 1.02–2.92, $p < 0.001$), and higher need for mechanical ventilation (OR = 2.34, 95% CI: 1.18–3.49, $p < 0.001$). Heterogeneity was high for mortality ($I^2 = 83.83\%$) but low for severity and mechanical ventilation ($I^2 = 0\%$). No significant publication bias was found.

**Conclusions** T2DM is associated with significantly worse outcomes in COVID-19 patients, including higher mortality, higher severity and a greater likelihood of needing mechanical ventilation. These findings emphasize the need for targeted interventions and management strategies for individuals with T2DM during the ongoing pandemic. Future research should focus on understanding the underlying mechanisms and exploring strategies to mitigate these risks.

**Keywords** COVID-19, Type 2 Diabetes Mellitus, Mortality, Disease severity, Mechanical ventilation, Meta-analysis

*Correspondence:
Stephen Olaide Aremu
dr.aresteph@gmail.com
Full list of author information is available at the end of the article

## Introduction

The COVID-19 pandemic has posed unprecedented challenges to global healthcare systems, straining resources and exposing vulnerabilities in healthcare infrastructures worldwide [1–5]. Among the most concerning aspects of the pandemic is its disproportionate impact on individuals with pre-existing health conditions, who face a higher risk of severe outcomes [6, 7]. Type 2 diabetes mellitus (T2DM), a chronic metabolic disorder characterized by insulin resistance and chronic hyperglycemia, has emerged as a key risk factor for severe COVID-19 outcomes [7, 8]. Beyond its long-term complications, such as cardiovascular disease and nephropathy, T2DM also impairs immune function, increasing susceptibility to infections, including SARS-CoV-2 [9].

The interplay between T2DM and COVID-19 has garnered significant attention, leading to numerous studies investigating its impact on disease severity, mortality, hospitalization rates, intensive care unit (ICU) admissions, and complications such as acute respiratory distress syndrome (ARDS) and thromboembolic events [10–12]. Initial findings suggest that individuals with T2DM are at heightened risk for severe COVID-19, but the magnitude of this risk varies across studies [13–15]. Some research indicates a significantly increased risk, while others report more moderate associations, highlighting inconsistencies in the literature [10–15]. This variability underscores the need for a comprehensive synthesis of existing evidence to clarify the true extent of the risk posed by T2DM in COVID-19 patients. Factors such as study design, population demographics, healthcare access, glycemic control, and coexisting conditions (e.g., hypertension and obesity) may contribute to these discrepancies [16–18]. Despite the growing body of research, there remains a lack of consensus on the precise impact of T2DM on COVID-19 outcomes and the factors that modulate this relationship.

To address these gaps, this study will conduct a systematic review and meta-analysis to quantify the association between T2DM and COVID-19 severity, mortality, hospitalization rates, and complications. Unlike previous studies that primarily focus on individual cohorts or single risk factors, this meta-analysis will integrate data from diverse populations and study designs to provide a more robust and generalizable understanding of the risks faced by individuals with T2DM. Additionally, it will explore key moderating factors, such as glycemic control, age, and comorbidities, to identify potential sources of heterogeneity in reported outcomes. By synthesizing and critically evaluating existing evidence, this study aims to fill critical knowledge gaps, support clinical decision-making, and inform public health policies. A clearer understanding of the T2DM-COVID-19 relationship will facilitate targeted interventions, improve risk stratification, and enhance healthcare strategies to protect this vulnerable population.

This study aims to systematically review and quantitatively analyze the impact of type 2 diabetes mellitus on COVID-19 outcomes, including disease severity, mortality, hospitalization rates, and complications, compared to individuals without type 2 diabetes mellitus. The first objective is: to determine the risk of severe COVID-19 outcomes, such as mortality, hospitalization, and ICU admission, in patients with T2DM, to investigate the association between T2DM and specific COVID-19 complications, including acute respiratory distress syndrome and thromboembolic events. Thirdly, to investigate potential moderators, such as age, sex, comorbidities, and glycemic control, that may influence the relationship between T2DM and COVID-19 outcomes. In addition, the quality and consistency of the evidence in the included studies should be assessed and sources of heterogeneity identified. Finally, to provide evidence-based recommendations for clinical practice and public health interventions aimed at mitigating the impact of COVID-19 in individuals with T2DM.

## Methodology

### Study design

This study was conducted as a systematic review and meta-analysis, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1). The aim was to evaluate the association between type 2 diabetes mellitus (T2DM) and adverse COVID-19 outcomes, including mortality, disease severity, and the need for mechanical ventilation.

### Search strategy

A comprehensive literature search was conducted across multiple databases, including PubMed, Scopus, Web of Science, Embase, Cochrane Library, Google Scholar, ClinicalTrials.gov, and MEDLINE**,** to identify relevant studies published between December 2019 and March 2024 (Table 1).

The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) to ensure broad coverage of relevant literature. The primary search terms included: COVID-19 (e.g., "COVID-19", "SARS-CoV-2", "coronavirus disease 2019"), Type 2 Diabetes Mellitus (e.g., "Type 2 Diabetes Mellitus", "T2DM", "diabetes and COVID-19"), Outcomes (e.g., "mortality", "severity", "mechanical ventilation", "ICU admission", "complications").

Boolean operators (AND, OR) were employed to refine and optimize the search, ensuring relevant studies were retrieved. The search was limited to peer-reviewed articles published in English**,** and only studies involving adult

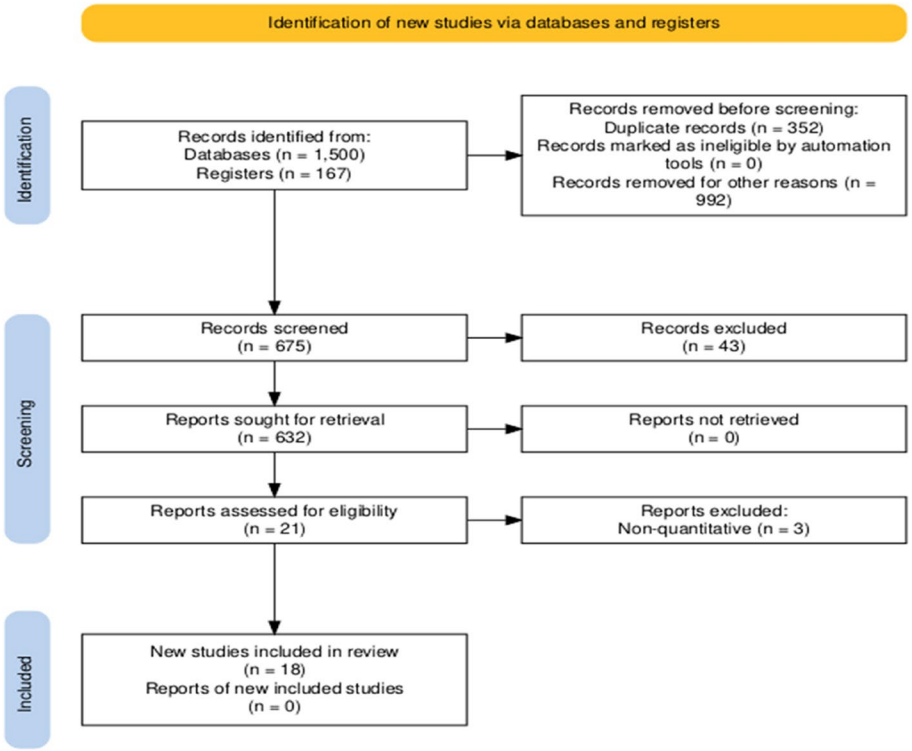


**Fig. 1** The PRISMA flow diagram shows the studies included in the meta-analysis for n number of studies

**Table 1** Search Terms and Boolean Combinations for Each Database

| Database | Search Terms & Boolean Combinations | Date of Last Search |
|---|---|---|
| PubMed | ("COVID-19" OR "SARS-CoV-2" OR "coronavirus disease 2019") AND ("Type 2 Diabetes Mellitus" OR "T2DM" OR "diabetes") AND ("mortality" OR "severity" OR "ICU admission" OR "mechanical ventilation" OR "complications") | January 18, 2024 |
| Scopus | TITLE-ABS-KEY ("COVID-19" OR "SARS-CoV-2") AND ("Type 2 Diabetes Mellitus" OR "T2DM") AND ("mortality" OR "severity" OR "critical illness" OR "hospitalization") | February 5, 2024 |
| Web of Science | TS = ("COVID-19" OR "SARS-CoV-2") AND TS = ("Type 2 Diabetes Mellitus" OR "T2DM") AND TS = ("mortality" OR "mechanical ventilation" OR "ARDS") | November 22, 2023 |
| Embase | ('COVID-19'/exp OR 'SARS-CoV-2'/exp) AND ('Type 2 diabetes mellitus'/exp OR 'T2DM'/exp) AND ('mortality'/exp OR 'hospitalization'/exp OR 'mechanical ventilation'/exp) | December 14, 2023 |
| Cochrane Library | ("COVID-19" OR "SARS-CoV-2") AND ("Type 2 Diabetes Mellitus" OR "T2DM") AND ("mortality" OR "ICU admission" OR "disease severity") | October 3, 2023 |
| Google Scholar | ("COVID-19" AND "Type 2 Diabetes Mellitus" AND "mortality") OR ("SARS-CoV-2" AND "T2DM" AND "complications") – Limited to title and first 200 results | March 1, 2024 |
| ClinicalTrials.gov | ("COVID-19" OR "SARS-CoV-2") AND ("Type 2 Diabetes Mellitus" OR "T2DM") – Filtered for completed and ongoing studies | January 30, 2024 |
| MEDLINE | ("COVID-19"[MeSH] OR "SARS-CoV-2"[MeSH]) AND ("Type 2 Diabetes Mellitus"[MeSH] OR "T2DM"[MeSH]) AND ("mortality"[MeSH] OR "severity"[MeSH] OR "hospitalization"[MeSH]) | February 12, 2024 |

populations (≥ 18 years) that reported on COVID-19 outcomes in individuals with T2DM were considered. To enhance reproducibility and transparency, a detailed search strategy, including specific search terms and Boolean combinations for each database, will be provided in a supplementary table. Additionally, reference lists of identified studies were manually screened to capture any relevant studies that may have been missed in the initial search. This approach ensures a systematic and rigorous selection of studies from diverse healthcare systems and

populations, thereby improving the generalizability of the findings on the relationship between T2DM and COVID-19 outcomes.

The search strategy applied filters to include only studies in English and those involving human subjects. Preprint servers such as medRxiv and bioRxiv were screened, and reference lists of relevant studies were manually reviewed. Both observational studies (cohort, case–control) and randomized controlled trials (RCTs) were considered for inclusion.

### Inclusion and exclusion criteria

#### *Inclusion criteria*

Studies were included based on the following criteria: they involved adult patients (≥ 18 years) diagnosed with COVID-19, examined the impact of Type 2 Diabetes Mellitus (T2DM) on COVID-19 outcomes, and reported at least one relevant outcome. These outcomes included mortality (e.g., in-hospital or 30-day mortality), disease severity (e.g., ICU admission, ARDS, critical illness), and the need for mechanical ventilation or advanced respiratory support.

#### *Study design*

The study design encompassed various observational studies, including prospective and retrospective cohort studies, case-control studies, and cross-sectional studies, provided they contained sufficient data for effect size calculation.

#### *Data availability*

Provided adequate data to calculate effect sizes (e.g., odds ratios [OR], relative risks [RR], hazard ratios [HR] with confidence intervals).

### Exclusion criteria

Studies were excluded if they focused on pediatric patients (< 18 years) or non-T2DM diabetic populations, such as those with Type 1 or gestational diabetes. Additionally, case reports, case series, narrative reviews, editorials, and commentaries were not considered. Animal studies and in vitro research were also excluded. Furthermore, studies with insufficient data for effect size estimation or those that did not report primary outcomes relevant to this analysis were omitted.

### Data extraction

Two independent reviewers extracted data from the included studies using a standardized data extraction form. The extracted data encompassed study characteristics such as author, year, country, and study design, as well as patient demographics, including sample size, age, and sex distribution. Additionally, information on T2DM status, including its presence, duration, and glycemic control when reported, was recorded. The key COVID-19 outcomes of interest, including mortality, disease severity, and the need for mechanical ventilation, were also extracted. Furthermore, effect sizes, such as odds ratios, relative risks, and hazard ratios, along with their corresponding confidence intervals, were collected to facilitate meta-analytic synthesis.

To ensure accuracy and consistency in the data extraction process, discrepancies between the two primary reviewers were initially addressed through discussion to reach a consensus. If disagreements persisted, a third independent reviewer was consulted to make the final decision, thereby minimizing subjectivity and ensuring a rigorous selection process. To further assess the reliability of the extraction process, Cohen's kappa (κ) was calculated to measure inter-rater agreement. A κ value of 0.80 or higher was considered indicative of strong agreement, while values between 0.61 and 0.79 suggested substantial agreement. Any studies with low agreement, defined as a κ value below 0.60, underwent re-evaluation to determine whether adjustments to the extraction protocol were necessary. This approach ensured the robustness of the data extraction process, minimized bias, and enhanced the overall transparency and reproducibility of the study.

### Quality assessment

The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS), a widely recognized tool for evaluating the methodological quality of observational studies. This scale is designed to assess three key areas: selection, comparability, and outcome assessment.

1. **Selection**: This domain examines how participants were selected for the study, including the representativeness of the study population and exposure ascertainment. The studies were evaluated based on criteria such as the definition of the study population, the appropriateness of the controls, and the selection process employed.
2. **Comparability**: This aspect focuses on the comparability of the study groups. It assesses whether the studies adequately controlled for potential confounding factors, such as age, gender, and other comorbidities (such as hypertension, obesity) that could influence the outcomes of interest. A higher score in this

area indicates better methodological rigor in the consideration of confounding factors.

3. **Outcome Assessment**: The final domain evaluates the methods used to assess outcomes, including the reliability and validity of the measurement tools employed. Studies were assessed on the clarity of outcome definitions, the timing of outcome assessment, and adequacy of follow-up to ascertain outcomes.

Each included study was assigned a score ranging from 0 to 9 based on its performance in these three domains. Studies that achieved a score of 7 or higher were considered to be of high quality, indicating that they possessed a strong methodological framework and were likely to produce reliable and valid results. This rigorous assessment ensured that the conclusions drawn from the meta-analysis were based on robust evidence, which increased the overall reliability of the findings regarding the interplay between type 2 diabetes mellitus and COVID-19 outcomes.

#### *Statistical analysis*

The meta-analyses were conducted using a random-effects model to account for potential heterogeneity among the included studies. This approach was selected because it allows for variability in true effect sizes across studies, acknowledging that differences in populations, interventions, and methodologies can influence the results. The $I^2$ statistic was employed to assess heterogeneity, with values greater than 50% indicating a significant heterogeneity among studies. Specifically, $I^2$ values of 25%, 50%, and 75% correspond to low, moderate, and high levels of heterogeneity, respectively. Furthermore, the $Tau^2$ estimator was utilized to quantify the variance between the studies. It provides a measure of between-study variance that complements the $I^2$ statistic.

Additionally, subgroup analyses were performed to explore potential sources of heterogeneity. These analyses focused on key demographic and clinical factors, including:

- **Patient Age**: Different age groups may exhibit varying responses to COVID-19. making it essential to analyze how age influences outcomes in individuals with type 2 diabetes mellitus (T2DM).
- **Gender**: As gender may have an impact on the severity of diabetes and COVID-19, subgroup analyses were stratified by male and female participants to identify potential differences in outcomes.
- **Glycemic Control**: The degree of glycemic control, as measured by metrics such as HbA1c levels, was assessed to determine its influence on the severity and mortality rate associated with COVID-19 in T2DM patients.
- **Geographical Location**: Differences in healthcare systems, population demographics and COVID-19 variants in different regions may influence the outcomes observed in the studies. Subgroup analyses were thus stratified based on geographical location to examine these effects.

To further evaluate the robustness of the findings, publication bias was assessed using several statistical methods. Egger's regression test was employed to quantitatively evaluate asymmetry in the funnel plot, with significant results indicating the presence of a publication bias. In addition, Kendall's Tau was used to assess the correlation between the effect sizes and their variances, providing information on the likelihood of bias in smaller studies. Finally, the Fail-safe N calculation was performed to estimate the number of additional studies with null results required to negate the overall effect observed in the meta-analysis, therefore evaluating the reliability of the conclusions drawn. Through these comprehensive analyses, the meta-analysis aimed to provide a nuanced understanding of the relationship between T2DM and COVID-19 outcomes while accounting for between study variability and potential bias.

#### *Outcome measures*

The primary outcomes were:

1. **Mortality:** The odds of death in COVID-19 patients with T2DM compared to patients without T2DM.
2. **Severity:** The odds of developing severe COVID-19 in patients with T2DM compared to non-diabetic patients.
3. **Mechanical Ventilation:** The odds of patients with T2DM requiring mechanical ventilation compared to patients without diabetes.

#### *Software*

All statistical analyses were performed using Jamovi software, version 2.6.13, with the "meta" package for meta-analysis.

#### *Reporting*

Results were reported as pooled odds ratios (ORs) with 95% confidence intervals (CIs). Forest plots (Fig. 2) were generated to visualize the effect sizes between studies,

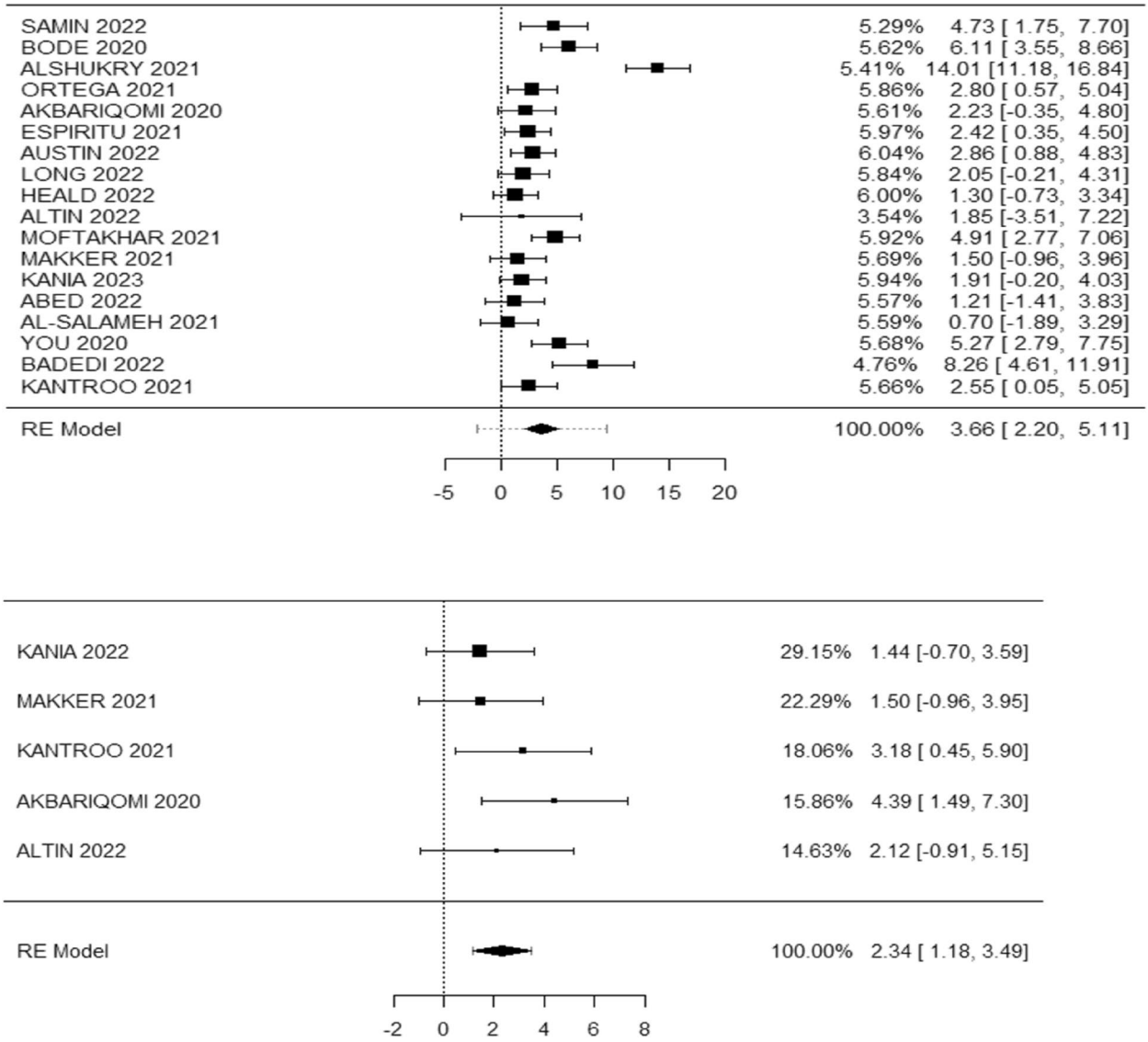


**Fig. 2** A forest plot showing the relationship between T2DM and **A** mortality in COVID-19, and **B** severity in COVID-19

and funnel plots were used to assess publication bias (Fig. 3).

#### *Sensitivity analysis*

Sensitivity analyses were performed by excluding low-quality studies and studies with extreme effect sizes to evaluate the robustness of the findings.

#### *Interpretation*

The results were interpreted in the context of existing literature, with comparisons drawn to similar recent studies to assess the consistency and reliability of the findings.

## Results

### Characteristics of the studies

The studies included in the systematic review and meta-analysis differed in several dimensions, such as study design, sample size and, the specifics of diabetes management and outcomes (Table 2).

#### *Study design and sample size*

Most studies were observational in design (e.g., retrospective or cross-sectional), with some including large cohorts (e.g., Austin et al., 2022, with 1,439,520 participants) [19]. Sample sizes ranged widely from smaller studies (e.g., Samin et al., 2022, with 120 patients) [20]

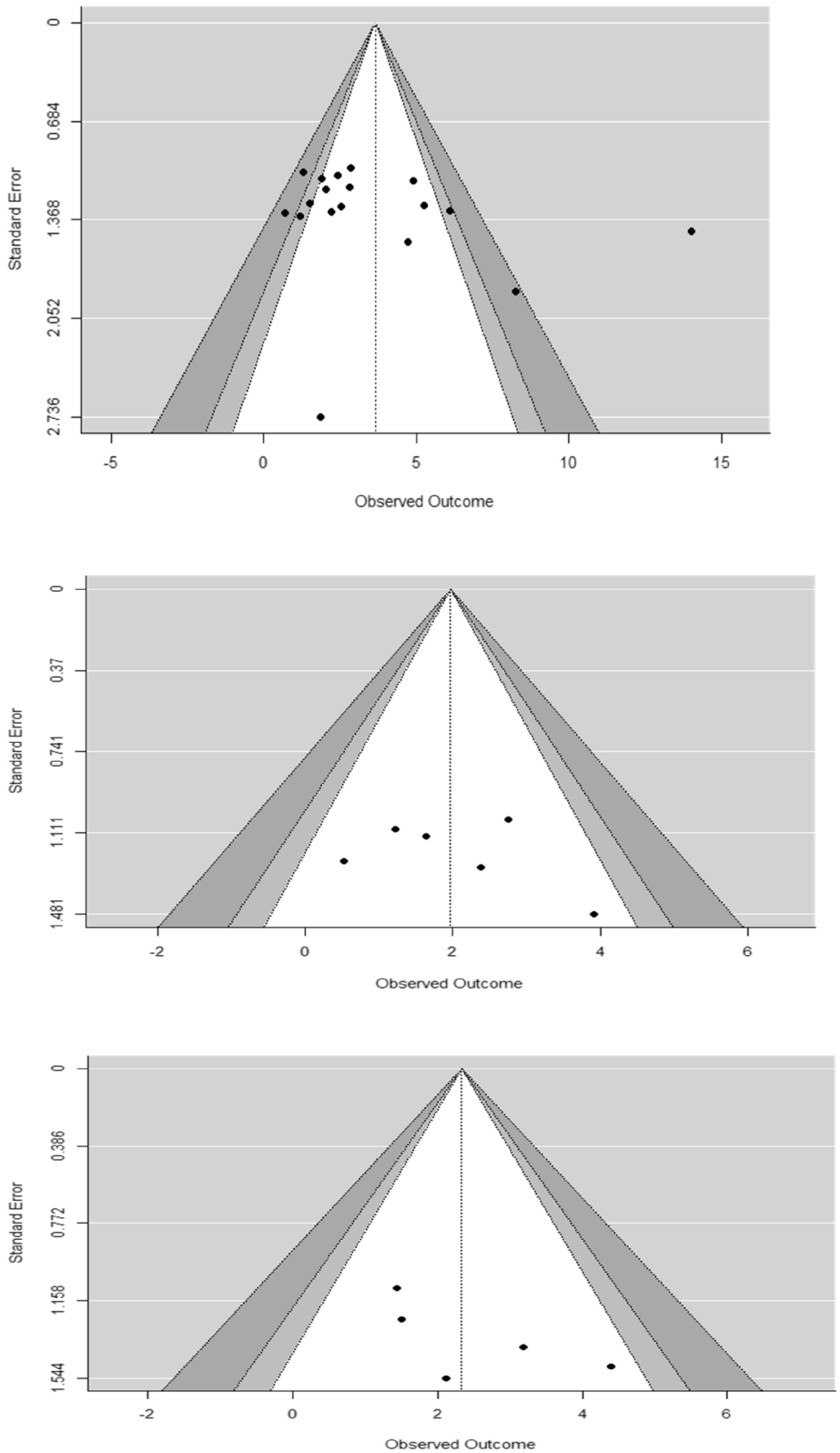


**Fig. 3** Funnel plots showing the association between T2DM and association between **A** mortality, **B** severity and **C** mechanical ventilation in COVID-19 patients

**Table 2** The features of articles included in the meta-analyses

| Author, Year | Country | Study design | Sample size (N) | Diabetes/Non Diabetes | Age | Comorbidities/ Complications | Symptoms | Mortality, Alive/ Recovered | Resource utilization | Effect size | Standard Error |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Samin et al., 2022 [20] | Pakistan | Retrospective/ Observational study | 120 | 70 diabetic patients (including 20 newly diagnosed with type II diabetes mellitus), 50 non-diabetic patients | Mean age of 48.14 ± 16.51 years | 52 cases (43.3%) had hypertension, 39 cases (32.5%) had cardiovascular diseases | Not explicitly detailed, but adverse outcomes and complications were measured | Mortality rate was higher in diabetic patients (57.1%) compared to non-diabetic patients (22%) | Diabetic patients had a significantly longer hospital stay compared to non-diabetic patients | 4.727 | 1.519 |
| Bode et al., 2020 [23] | United States | Retrospective observational study | 887 | 451 patients with diabetes and/ or uncontrolled hyperglycemia, 386 patients without diabetes or hyperglycemia | Not specified | Diabetes, uncontrolled hyperglycemia (defined as ≥ 2 blood glucose readings > 180 mg/ dL within any 24-h period) | Glycemic control issues among hospitalized COVID-19 patients; data focused on blood glucose levels | Mortality rate was 28.8% in diabetes and/ or uncontrolled hyperglycemia patients compared to 6.2% in patients without these conditions; 41.7% mortality in uncontrolled hyperglycemia patients, 14.8% in diabetes patients | Longer median length of stay (LOS) for patients with diabetes and/or uncontrolled hyperglycemia (5.7 days) compared to patients without these conditions (4.3 days) | 6.107 | 1.304 |
| Alshukry et al., 2021 [22] | Kuwait | Single-center, retrospective study | 417 | The study compares diabetic and non-diabetic COVID-19 patients | The study does not specify the age distribution, but age-related details might have been considered in relation to outcomes | Diabetic COVID-19 patients had a significantly higher prevalence of comorbidities, particularly hypertension. They also showed higher levels of C-reactive protein and lower estimated glomerular filtration rates, indicating more severe complications | The study did not specifically detail the symptoms but highlighted that diabetic patients experienced more severe disease outcomes | Diabetic COVID-19 patients had significantly higher ICU admission rates (42.4% vs. 7.7%) and mortality rates (34.7% vs. 3.7%) compared to non-diabetic patients | Diabetic COVID-19 patients required more intensive care, as indicated by higher ICU admissions and an increased need for managing complications associated with diabetes. Every 1 mmol/L increase in fasting blood glucose was associated with a 1.52 times higher risk of mortality from COVID-19 | 14.01 | 1.443 |
| Ortega et al., 2022 [24] | Spain | Cross-sectional study | 2,069 | The study compared outcomes between patients with and without diabetes | | The study found that diabetes was independently associated with higher mortality and the need for invasive mechanical ventilation (IMV). Key factors associated with poor outcomes in diabetic patients included being over 65 years old, | Specific symptoms were not detailed in the summary, but the study focused on severe in-hospital complications | The overall in-hospital mortality was 18.6%, with higher mortality among patients with DM (26.3%) compared to those without DM (11.3%). Diabetes was associated with a higher risk of death (OR = 2.33) and death or IMV (OR = 2.11) | Higher blood glucose levels on admission were associated with worse outcomes, suggesting the need for personalized glycemic optimization to improve outcomes during hospitalization | 2.804 | 1.142 |

**Table 2** (continued)

| Author, Year | Country | Study design | Sample size (N) | Diabetes/Non Diabetes | Age | Comorbidities/ Complications | Symptoms | Mortality, Alive/ Recovered | Resource utilization | Effect size | Standard Error |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | male, and having pre-existing chronic kidney disease. There was a non-linear relationship between admission blood glucose levels and the risk of in-hospital mortality or death/IMV | | | | | |
| Akbariqomi et al., 2020 [25] | Iran | Retrospective, single-center study | 595 | The study included 148 patients with diabetes (24.9%) and compared them to 447 patients without diabetes | The median age of the patients was 55 years | Diabetic patients had more comorbidities, particularly hypertension (48.6% vs. 22.3%). They also exhibited higher levels of white blood cell count, neutrophil count, C-reactive protein, erythrocyte sedimentation rate, and blood urea nitrogen. Diabetic patients had a higher proportion of patchy ground-glass opacity in chest CT scans (52.7% vs. 25.7%). Complications were more common, and the need for respiratory support was higher among diabetic patients | The most common symptoms were fever (70.4%), dry cough (61.8%), and dyspnea (61%) | Mortality was significantly higher in patients with diabetes (17.8%) compared to those without diabetes (8.7%) | Patients with diabetes required more respiratory support and had a higher rate of treatment failure compared to non-diabetic patients | 2.229 | 1.314 |
| Espiritu et al., 2021 [28] | Philippines | Nationwide, comparative, retrospective cohort study | 10,881 | Diabetes/Non-Diabetes: 2,191 patients with diabetes (DM) and 8,690 without diabetes (non-DM) | Median age of DM cohort was 61 years, with over 50% above 60 years old; female-to-male ratio was 1:1.25 | Focused on diabetes mellitus (DM) | Not explicitly detailed, but adverse outcomes and complications were measured | Mortality: Adjusted odds ratio (aOR) for mortality in the DM group was significantly higher at 1.46 (95% CI 1.28–1.68; $p < 0.001$) compared to the non-DM group Respiratory Failure: aOR for respiratory failure was 1.67 (95% CI 1.46–1.90) | The presence of diabetes mellitus (DM) in COVID-19 patients significantly increased the risk of mortality, respiratory failure, severe/critical COVID-19, ICU admission, ventilator dependence, and longer hospital stays compared to non-DM patients | 2.423 | 1.06 |

**Table 2** (continued)

| Author, Year | Country | Study design | Sample size (N) | Diabetes/Non Diabetes | Age | Comorbidities/ Complications | Symptoms | Mortality, Alive/ Recovered | Resource utilization | Effect size | Standard Error |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | higher in the DM group<br>Severe COVID-19: aOR for developing severe/critical COVID-19 was 1.85 (95% CI 1.65–2.07; p < 0.001) higher in the DM group<br>ICU Admission: aOR for ICU admission was 1.80 (95% CI 1.59–2.05) higher in the DM group<br>Ventilator Dependence: DM patients had significantly longer duration of ventilator dependence (aOR 1.33, 95% CI 1.08–1.64; p = 0.008)<br>Length of Hospital Stay: DM patients had longer hospital admissions (aOR 1.13, 95% CI 1.01–1.26; p = 0.027) | | | |
| Austin et al., 2022 [19] | United States | Observational cohort study | 1,439,520 | The study compares COVID-19 outcomes between beneficiaries with and without diabetes mellitus | Diabetic beneficiaries were younger compared to non-diabetic beneficiaries | Diabetic beneficiaries had more comorbidities, higher rates of Medicare-Medicaid dual eligibility, and were more likely to be Black<br>They also had worse hospitalization outcomes, including higher rates of ICU admissions and in-hospital complications | The study focuses on disease severity and outcomes rather than specific symptoms | Diabetic beneficiaries had higher overall mortality following a COVID-19 diagnosis (17.3% vs. 14.9%) | Diabetic beneficiaries had higher hospitalization rates (20.5% vs. 17.1%), more ICU admissions (7.78% vs. 6.11%), more ambulatory care visits (8.9 vs. 7.8), and higher ICU mortality (2.41% vs. 1.77%) | 2.857 | 1.007 |
| Long et al., 2022 [29] | Not specified | Multicenter study | 2,330 | 336 patients with diabetes mellitus (DM), 1344 non-diabetic patients matched by age and sex | Age-stratified analysis conducted (specific age range not provided) | Higher rates of intensive care unit (ICU) admission (12.43% vs. 6.58%), kidney failure (9.20% vs. 4.05%), and mortality (25.00% vs. 18.15%) in DM patients compared to non-DM patients; hyperglycemia was associated with adverse outcomes in both DM and non-DM patients | Severe pneumonia associated with hyperglycemia | Mortality was higher in DM patients (25.00%) compared to non-DM patients (18.15%); hazard ratios for adverse prognosis were 10.41 for diabetes and 3.58 for hyperglycemia | Higher ICU admission rates and increased laboratory abnormalities (e.g., lymphocyte and neutrophil percentage, C-reactive protein, urea nitrogen) in DM and hyperglycemic patients | 2.046 | 1.153 |

**Table 2** (continued)

| Author, Year | Country | Study design | Sample size (N) | Diabetes/Non Diabetes | Age | Comorbidities/ Complications | Symptoms | Mortality, Alive/ Recovered | Resource utilization | Effect size | Standard Error |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Heald et al., 2022 [27] | United Kingdom | Urban population study using electronic health record data | 53,390 | Diabetes: 13,807 individuals with type 2 diabetes mellitus (T2DM)<br>Non-Diabetes Controls: 39,583 COVID-19-infected individuals without diabetes | The study does not provide specific age details but included a broad population in Greater Manchester | Increased Mortality Risk: Higher in those with chronic obstructive pulmonary disease (COPD), severe enduring mental illness, and those taking aspirin/clopidogrel/insulin<br>Associated with Higher Mortality: Lower estimated glomerular filtration rate (eGFR), hypertension, smoking<br>Protective Factors: Taking metformin, sodium-glucose cotransporter 2 inhibitors (SGLT2i), or glucagon-like peptide 1 (GLP-1) agonists was associated with reduced mortality risk | The study did not specify symptoms but focused on mortality and associated factors | Mortality Rate for T2DM: 7.7% after a positive COVID-19 test<br>Mortality Rate for Non-Diabetes Controls: 6.0%<br>Relative Risk (RR) of Death for T2DM: 1.28 compared to non-diabetes controls | Predictive Factors for Higher Mortality: Age, male gender, and social deprivation (higher Townsend score) were significant<br>Protective Measures: Prescription of specific medications (metformin, SGLT2i, GLP-1 agonists) and non-smoking status were associated with reduced mortality risk | 1.305 | 1.039 |
| Altin et al., 2022 [26] | Turkey | Retrospective observational study | 341 | Diabetic: 120 patients<br>Non-Diabetic: 221 patients | Not specified | More susceptible to severe COVID-19 infection and increased need for oxygen therapy<br>Poorly Controlled Diabetes: Associated with longer hospitalization compared to well-controlled diabetes | Severe disease (47.5% in diabetics vs. 27.8% in non-diabetics), higher need for oxygen therapy (51.2% in diabetics vs. 29.4% in non-diabetics) | No significant difference in mortality rates between diabetic and non-diabetic patients | Diabetic patients had a median hospitalization duration of 8 days (longer than non-diabetics at 7 days). Poorly controlled diabetic patients had a longer median hospitalization duration (9 days) compared to well-controlled diabetic patients (8 days)<br>Intensive monitoring and disease management recommended for diabetic patients with comorbidities | 1.855 | 2.736 |
| Moftakhar et al., 2021 [21] | Iran | Retrospective observational study | 16,391 | 1,365 individuals with diabetes<br>15,026 individuals without diabetes | Diabetic Patients: Average age of 59 years<br>Non-Diabetic Patients: Average age of 37 years | Higher in Diabetic Patients: Hypertension, cardiovascular disease, chronic lung disease, immune deficiency, and hyperlipidemia<br>Increased Symptoms: Fever, cough, shortness of breath, headache | Higher odds of fever, cough, shortness of breath, and headache compared to non-diabetic patients | Diabetic Mortality Rate: 14.3%<br>Proportion of Deaths in Diabetics: 28.3% of COVID-19-related deaths occurred in diabetic patients | Public Health Challenge: Diabetes significantly increases mortality from COVID-19, highlighting the need for targeted prevention and treatment strategies for diabetic patients | 4.911 | 1.094 |

**Table 2** (continued)

| Author, Year | Country | Study design | Sample size (N) | Diabetes/Non Diabetes | Age | Comorbidities/ Complications | Symptoms | Mortality, Alive/ Recovered | Resource utilization | Effect size | Standard Error |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Makker et al., 2021 [30] | Not specified (Single-center study) | Retrospective observational study | 733 | Patients were categorized into three groups: control (non-diabetic), prediabetes, and type-2 diabetes | Key stratification at 55 years Mortality and mechanical ventilation use compared among younger (< 55 years) and older (≥ 55 years) patients | Type-2 diabetes, prediabetes, newly diagnosed vs. previously diagnosed diabetes | Not detailed; focus on clinical outcomes such as mortality and mechanical ventilation | Older patients (≥ 55 years): No significant difference in mortality or mechanical ventilation among control, prediabetes, and type-2 diabetes groups<br>Younger patients (< 55 years): Higher mortality in type-2 diabetes group (27%) compared to control (9%) and prediabetes (12.5%)<br>Newly diagnosed type-2 diabetes: Lower mortality (18%) compared to previously known type-2 diabetes patients (40%)<br>Prediabetes: Outcomes similar to the control group | Admission hyperglycemia is associated with higher mortality regardless of diabetes status | 1.502 | 1.255 |
| Kania et al., 2023 [31] | Poland | Retrospective study | 5,191 | The study included 1,364 diabetic patients (26.3%) and compared them with non-diabetic patients | Diabetic patients were older (median age 70 years) compared to non-diabetics (median age 62 years) | Diabetic patients had higher rates of comorbidities such as heart failure and chronic kidney disease Risk factors associated with higher mortality included age >65 years, glycemia > 10 mmol/L, elevated CRP and D-dimer levels, and prehospital use of insulin and loop diuretics | The study focused on outcomes rather than specific symptoms | Diabetic patients had a higher mortality rate (26.2% vs. 15.7%, $p < 0.001$) and longer hospital stays. Factors contributing to lower mortality included the in-hospital use of statins, thiazide diuretics, and calcium channel blockers | Diabetic patients required more intensive care, including higher rates of ICU admission (15.7% vs. 11.0%) and mechanical ventilation (15.5% vs. 11.3%). They also had longer hospital stays compared to non-diabetics | 1.913 | 1.079 |
| Abed et al., 2022 [32] | Algeria | Observational study | 285 | 48.80% of the patients in the sample had diabetes<br>The rest had no mention of diabetes, implying non-diabetic or unspecified status | Average age of diabetic patients: 62.53 ± 16.65 years | High CRP levels in 95.7%<br>Hyperglycemia in 64%<br>Hyperleukocytosis in 26.6%<br>Elevated D-dimer in 56%<br>Hypoprothrombinemia in 21.6% | Oxygen desaturation in 64.7%<br>Important or critical pulmonary affliction in 28.8% and 18.7%, respectively | Mortality rate among diabetic patients: 22.3%<br>The report does not specify the exact number of patients alive or recovered, only the mortality rate | The study emphasizes the need for improved care for diabetic patients due to high infection rates, biological abnormalities, and mortality | 1.21 | 1.339 |

**Table 2** (continued)

| Author, Year | Country | Study design | Sample size (N) | Diabetes/Non Diabetes | Age | Comorbidities/ Complications | Symptoms | Mortality, Alive/ Recovered | Resource utilization | Effect size | Standard Error |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | High urea levels in 36.7% Hypo-creatinemia in 12% Elevated ASAL and ALAT in 28.8% and 26.6%, respectively | | | | | |
| Al-Salameh et al., 2021 [33] | France | Retrospective cohort study | 432 | 115 patients with diabetes (26.6%), 318 patients without diabetes (73.4%) | Median age of 72 years | Diabetes, older age associated with higher mortality; diabetes associated with longer hospital stay and higher ICU admission | Not detailed, focus on clinical outcomes such as ICU admission and mortality | Diabetes was not significantly associated with mortality (HR: 0.73; 95% CI: 0.40–1.34), but was associated with ICU admission (OR: 2.06; 95% CI: 1.09–3.92, P =.027) | Diabetes was associated with a greater risk of ICU admission and a longer hospital stay; age was negatively associated with ICU admission and positively associated with mortality | 0.703 | 1.322 |
| You et al., 2020 [34] | Korea | Retrospective cohort study | 5,473 | 495 patients with type 2 diabetes, 4,978 patients without diabetes | Not specified, but adjustment for age was made in the analysis | Comorbidities adjusted for in the analysis, higher likelihood of ICU admission for diabetes patients | Not explicitly detailed, but focus on ICU admission, in-hospital mortality, and clinical outcomes | Higher in-hospital mortality for diabetes patients (P < 0.0001); adjusted odds ratio for mortality was 1.90 (95% CI, 1.13 to 3.21, P = 0.0161) | Higher odds of ICU admission for diabetes patients (adjusted OR 1.59, 95% CI 1.02 to 2.49, P = 0.0416); no significant difference in ventilator use, oxygen therapy, antibiotics, antiviral drugs, antipyretics, or incidence of pneumonia after adjustment | 5.27 | 1.267 |
| Badedi et al.,2022 [35] | Saudi Arabia | Retrospective cohort study | 412 | The study included patients with type 2 diabetes mellitus (T2DM) compared to those without T2DM | Not specified, but the study focused on adult patients | COVID-19 patients with T2DM had increased blood glucose levels, requiring higher insulin doses. They were also more likely to have severe complications, such as an oxygen saturation of ≤ 90%, and were more frequently admitted to the intensive care unit (11% vs. 5%) | Most patients with T2DM exhibited clinical COVID-19 symptoms (91%), while 9% were asymptomatic. Those with mild symptoms often self-isolated at home (80%) | Mortality was higher in COVID-19 patients with T2DM (9%) compared to those without T2DM (1%) | COVID-19 patients with T2DM required more intensive care and increased insulin doses during their hospital stay. The disease duration was also longer for T2DM patients compared to non-diabetic patients (10.7 days vs. 8.3 days) | 8.26 | 1.864 |

**Table 2** (continued)

| Author, Year | Country | Study design | Sample size (N) | Diabetes/Non Diabetes | Age | Comorbidities/ Complications | Symptoms | Mortality, Alive/ Recovered | Resource utilization | Effect size | Standard Error |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kantroo et al., 2021 [36] | India | Retrospective study | 1,192 | 26.8% of the patients had diabetes mellitus (DM) | Increased age was associated with higher mortality | The study identified several comorbidities significantly associated with mortality, including chronic kidney disease (CKD), coronary artery disease (CAD), stroke, and cancer. CAD, CKD, and cancer were independent predictors of mortality | Patients who presented with breathlessness, low oxygen saturation (SpO2), extensive lung involvement on chest X-ray (CXR), and an elevated absolute neutrophil count/absolute lymphocyte count (ANC/ALC) ratio were more likely to experience severe outcomes | The overall mortality rate was 6.1%, and it was higher in patients with diabetes (10.7%) | Early triaging and aggressive therapy were recommended to optimize clinical outcomes for patients with comorbidities such as DM, hypertension, CAD, CKD, and cancer | 2.552 | 1.227 |

to large cohorts (e.g., Moftakhar et al., 2021, with 16,391 patients) [21].

#### *Diabetes and non-diabetes groups*

Most studies compared outcomes between patients with type 2 diabetes mellitus (T2DM) and those without diabetes. Diabetic patients often had more comorbidities and complications, which were generally described in detail (e.g., Alshukry et al., 2021 [22], reported significant comorbidities such as hypertension in diabetic patients).

#### *Outcomes assessed*

Studies assessed various outcomes, including mortality, severity of illness, need for mechanical ventilation, and ICU admission. For example, Bode et al., 2020 [23], highlighted higher mortality rate and longer hospital stays in diabetic patients. Studies, such as Ortega et al., 2022 [24], focused on the relationship between blood glucose levels and treatment outcomes and showed demonstrating the impact of glycemic control on mortality and the need for mechanical ventilation.

#### *Effect size and resource utilization*

Effect sizes varied among studies, with many showing a significant increase in mortality and resource utilization in diabetic patients (e.g., Akbariqomi et al., 2020 [25], showing a higher mortality rate in diabetic patients).

### Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to assess study quality. The included studies varied in quality but generally met high standards.

#### *Selection and comparability*

Studies with higher NOS scores (e.g., Alshukry et al., 2021, with a score of 14.01) were well-designed and had rigorous selection criteria and comparability between diabetic and non-diabetic groups. Some studies had lower NOS scores, including possible limitations in sample size or methodological rigor (e.g., Altin et al., 2022, with a score of 1.855) [26].

#### *Outcome assessment*

Most studies reported comprehensive outcome data on, although some did not provide detailed information on specific symptoms (e.g., Heald et al., 2022) [27]. The quality was reflected in the robustness of the effect sizes and the precision of the estimates. Espiritu et al., 2021 [28], for example, provided detailed adjusted odds ratios for various adverse outcomes.

#### *Inclusion and exclusion criteria*

All studies adhered to the inclusion criteria i.e. they focused on adult COVID-19 patients and examined the impact of T2DM on outcomes. However, some had limitations related to missing data or a lack of detail on certain aspects, which affected their quality assessment. The exclusion criteria were well followed, excluding case reports and studies with incomplete data.

In general, the studies provide a detailed overview of the impact of T2DM on COVID-19 outcomes. High-quality studies generally showed a clear association between diabetes and increased adverse outcomes, while studies with lower NOS scores may have had methodological weaknesses that should be considered when interpreting their findings.

In the present meta-analysis, three key outcomes were evaluated to assess the relationship between type 2 diabetes mellitus (T2DM) and COVID-19 outcomes: mortality, severity of illness, and the need for mechanical ventilation. The analysis utilized a random-effects model across various studies, and rigorous heterogeneity and publication bias assessments were performed to ensure the robustness of the results (Table 3).

### Mortality

The random-effects model incorporating data from 18 studies, found a significant association between T2DM and increased mortality in COVID-19 patients (Fig. 3). The model estimated an effect size of 3.6553 (SE = 0.7444), with a Z-value of 4.9103 and a p-value < 0.001, indicating a robust and statistically significant effect. The 95% (CI) of 2.1963 to 5.1143 further confirms the increased mortality risk in COVID-19 patients with T2DM. These results indicate that individuals with T2DM have significantly higher risk of death when infected with COVID-19 than individuals without T2DM.

Heterogeneity analysis yielded a $Tau^2$ value of 8.1587 (SE = 3.4058) and an $I^2$ statistic of 83.83%, indicating substantial heterogeneity across studies. This indicates considerable variability in effect sizes among the included studies, likely due to differences in study populations, settings, or methodologies. The Q-Statistic of 89.4414 ($p < 0.001$) further supports the presence of statistically significant heterogeneity. Nevertheless, the Fail-Safe N of 905 suggests that a large number of additional studies with null results would be required to invalidate the observed effect, providing further confidence in the robustness of the findings. Additionally, Kendall's Tau (0.2157, $p = 0.229$) and Egger's Regression (0.8804, $p = 0.379$) indicate that there is no significant publication bias, affirming the validity of the results.

**Table 3** Summary of Random-Effects Models, Heterogeneity, and Publication Bias for Mortality, Severity, and Mechanical Ventilation in T2DM and COVID-19 studies

| Outcome | Estimate | SE | Z | p | CI Lower Bound | CI Upper Bound | $Tau^2$ (SE) | $I^2$ | $H^2$ | Q (df) | p (Q) | Fail-Safe N | Kendall's Tau | p (Kendall's) | Egger's Regression | p (Egger's) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mortality (k = 18) | 3.6553 | 0.7444 | 4.9103 | <.001 | 2.1963 | 5.1143 | 8.1587 (3.4058) | 83.83% | 6.1860 | 89.4414 (17) | <.001 | 905 | 0.2157 | 0.229 | 0.8804 | 0.379 |
| Severity (k = 6) | 1.9692 | 0.4844 | 4.0650 | <.001 | 1.0197 | 2.9187 | 0 (0.8819) | 0% | 1.0000 | 4.3127 (5) | 0.505 | 32 | 0.2000 | 0.719 | 0.7853 | 0.432 |
| Mechanical ventilation (k = 5) | 2.3351 | 0.5907 | 3.9533 | <.001 | 1.1774 | 3.4928 | 0 (1.2263) | 0% | 1.0000 | 3.4275 (4) | 0.489 | 26 | 0.6000 | 0.233 | 1.2936 | 0.196 |

$Tau^2$ Estimator: Restricted Maximum-Likelihood

Fail-Safe N: Calculation using the Rosenthal Approach

### Severity of illness

The analysis of the severity of COVID-19 in patients with T2DM based on data from six studies also demonstrated a significant association (Fig. 3). The random-effects model estimated an effect size of 1.9692 (SE = 0.4844), with a Z-value of 4.0650 and a p-value < 0.001, indicating that T2DM is associated with more severe illness in COVID-19 patients. The 95% CI, ranging from 1.0197 to 2.9187, underscores the robustness of this association.

In contrast to the mortality outcome, the heterogeneity analysis for severity showed no observed heterogeneity, with a $Tau^2$ of 0 and an $I^2$ of 0%. The Q statistic (4.3127, p = 0.505) confirmed the absence of significant variability across studies, suggesting consistent findings. The Fail-Safe N of 32 indicates that a moderate number of studies with null-results would be required to challenge the observed effect, further supporting the strength of the evidence. Publication bias assessments, including Kendall's Tau (0.2000, p = 0.719) and Egger's Regression (0.7853, p = 0.432), also showed no significant bias, indicating that the results are unlikely to be influenced by selective reporting.

### Need for mechanical ventilation

A similar pattern was observed regarding the need for mechanical ventilation in COVID-19 patients with T2DM (Fig. 3). Data from five studies showed a significant association, with an estimated effect size of 2.3351 (SE = 0.5907), a Z-value of 3.9533, and a p-value < 0.001. The 95% CI ranged from 1.1774 to 3.4928, supporting the conclusion that T2DM significantly increases the likelihood of needing mechanical ventilation.

As with the severity outcome, no heterogeneity was found in this analysis ($Tau^2$ = 0, $I^2$ = 0%). The Q statistic (3.4275, p = 0.489) confirmed the absence of significant heterogeneity across the studies. The Fail-Safe N of 26 suggests that a small, but significant, number of studies with null results would be required to negate the observed effect. Both Kendall's Tau (0.6000, p = 0.233), and Egger's regression (1.2936, p = 0.196) indicated no significant publication bias. Finally, equivalence testing by two one-sided tests revealed a significant lower bound (Z = 4.7998, p < 0.001), supporting the meaningful association between T2DM and increased need for mechanical ventilation.

The pooled effect under the common effect model shows a significant negative effect (− 9.38), indicating a consistent effect direction across studies (Fig. 4). However, due to high heterogeneity, the random effects model is more appropriate. The random effects model yields a less precise pooled estimate (− 6.95), and its CI crosses zero, suggesting that the overall effect may not be statistically significant when accounting for the variability across studies. The significant heterogeneity indicates that the

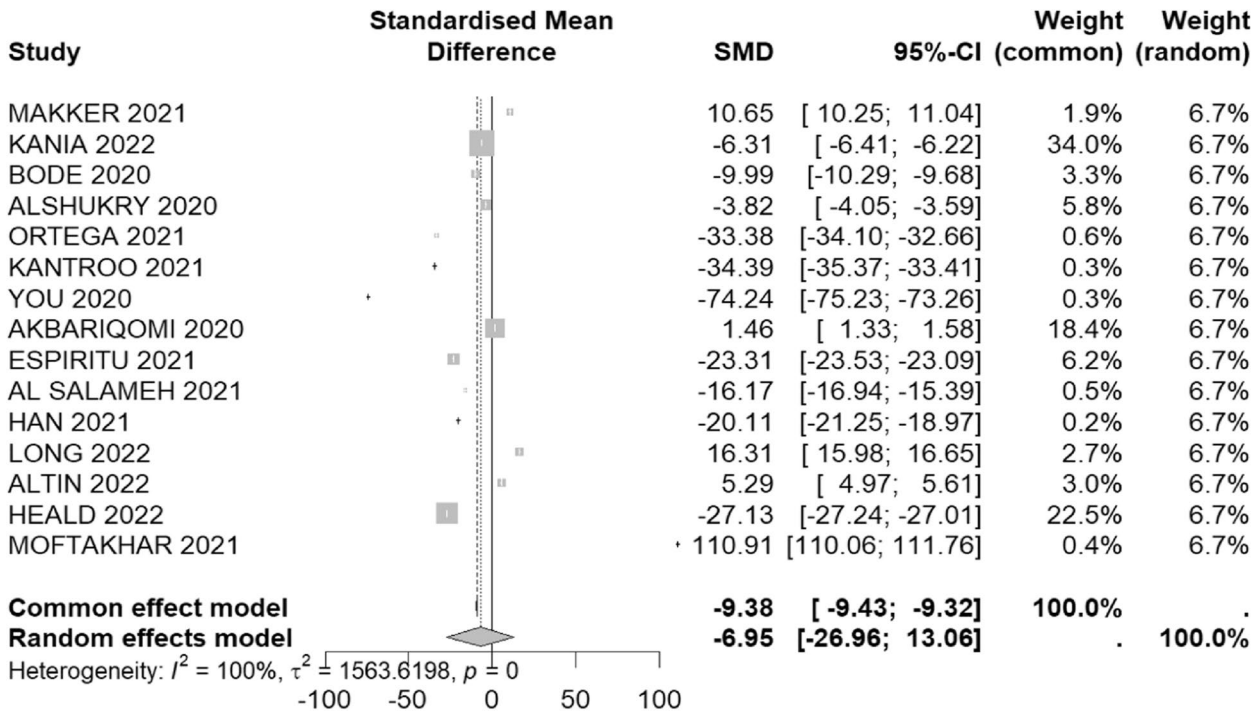


**Fig. 4** Forest Plot of Standardized Mean Differences: Meta-Analysis of Study Effect Sizes with High Heterogeneity according to mortality

studies are not entirely comparable, and the effects likely vary across different study contexts or populations.

## Discussion

Type 2 diabetes mellitus (T2DM) is a known risk factor for severe outcomes in various infectious diseases [37–40], and its role in the context of COVID-19 has attracted considerable attention [41–45]. As observed in several studies, the presence of T2DM in patients with COVID-19 significantly increases the risk of mortality, severity and need for mechanical ventilation [40, 41]. The interrelationship between these conditions stems from the complex pathophysiological mechanisms underlying both T2DM and COVID-19, leading to exacerbated immune responses, increased inflammatory states and impaired pulmonary and cardiovascular functions [46–49].

### Mortality and severity

Several studies have confirmed that individuals with T2DM have an increased risk of developing severe COVID-19 [50–52]. A meta-analysis conducted by Bradley et al. (2022) [41] revealed that diabetics have a higher mortality when hospitalized with COVID-19 compared to non-diabetics [41]. T2DM patients, especially those with poor glycemic control, tend to have an exaggerated inflammatory response. This inflammatory state, characterized by elevated cytokine levels such as interleukin-6 (IL-6), contributes to the cytokine storm observed in severe COVID-19 cases, and increased the likelihood of complications such as acute respiratory distress syndrome (ARDS), multi-organ failure and subsequent death [12, 53, 54].

Hyperglycemia, a hallmark of diabetes, is associated with impaired immune response via the alteration of cytokine and leukocyte response, leading to increased viral replication, and dysregulated coagulation pathways that exacerbate the severity of COVID-19. Dysfunctional neutrophil activity, reduced T-cell response, and impaired macrophage function contribute to the increased severity of infections in diabetics. These immunological alterations may explain why diabetics experience more severe COVID-19 outcomes [12]. Additionally, the gut microbiome plays a crucial role in immune homeostasis, and its alterations in diabetics could influence COVID-19 severity by modulating systemic inflammation and immune function [54].

Moreover, diabetic patients often have comorbidities such as hypertension and cardiovascular disease, both of which have been independently associated with poorer outcomes in COVID-19. As Tadic et al. discuss, hypertension, which often accompanies T2DM, remains a controversial but significant factor that can exacerbate the severity of COVID-19, further complicating disease progression and increasing the mortality risk. More so, Emerging evidence suggests that viral replication, viral load, and persistence may differ in diabetics compared to non-diabetics. Hyperglycemia may create an environment conducive to prolonged viral shedding and increased viral burden. These differences in viral dynamics may be driven by both metabolic factors and immune dysregulation, warranting further investigation [52].

### Mechanical ventilation

Mechanical ventilation is a crucial measure in patients who develop severe respiratory complications due to COVID-19, particularly in patients with ARDS [55]. It has been observed that diabetic patients require mechanical ventilation more frequently than their non-diabetic counterparts due to their predisposition to severe lung involvement [56, 57]. Tzotzos et al. (2020) [43] demonstrated that diabetic individuals were overrepresented among COVID-19 patients who developed ARDS, a condition necessitating advanced ventilatory support [58]. The combination of hyperglycemia, immune dysfunction, and chronic inflammation in T2DM contributes to respiratory compromise and necessitates mechanical ventilation in severe cases [59–61].

Myocardial injury, which is common in severe COVID-19 patients with diabetes, also plays a crucial role in the need for mechanical ventilation. Metkus et al. (2020) [44] highlighted that myocardial injury in COVID-19 patients with T2DM occurs more frequently than in non-diabetic individuals with ARDS due to non-COVID-19 causes. The interplay between cardiovascular complications and lung failure in diabetic COVID-19 patients places significant strain on the airway of the respiratory systems, leading to an elevated need for ventilatory support [54]. Furthermore, pre-existing diabetic vascular complications, such as endothelial dysfunction and microvascular injury, are exacerbated by the thrombotic and inflammatory processes associated with COVID-19, contributing to poor oxygenation and increased mechanical ventilation requirements [55]. As noted by Gęca et al. (2022) [12] this exacerbation leads to a higher risk of respiratory failure and mortality, particularly in patients with poorly controlled T2DM [11].

Overall, these findings contribute to the growing body of evidence highlighting the importance of managing T2DM in the context of COVID-19. They reinforce the need for targeted interventions, such as stringent glycemic control, personalized treatment approaches for comorbid conditions, and potential use of anti-inflammatory therapies to improve outcomes in this vulnerable population [50]. While the results align with existing theories on the impact of metabolic dysfunction

in infectious diseases, they also present new avenues for exploration, particularly regarding the interplay between diabetes, immune response, and cardiovascular complications in viral infections. Future studies should aim to elucidate these mechanisms further, incorporating prospective designs and interventional approaches to refine our understanding of how T2DM shapes COVID-19 severity and mortality.

## Limitations of the study

The study on the association between T2DM and COVID-19 mortality, severity, and mechanical ventilation has several limitations that must be acknowledged. A major limitation is the substantial heterogeneity among the included studies in terms of population demographics, healthcare systems, and treatment protocols, which can significantly affect the generalizability of the findings. Differences in the availability and quality of healthcare resources, variations in diagnostic criteria, and disparities in access to intensive care may have contributed to inconsistencies in reported outcomes. Another key limitation is the presence of confounding factors, particularly comorbid conditions such as hypertension, obesity, and cardiovascular disease, which frequently coexist with T2DM. While some studies attempted to adjust for these factors, the extent to which they were adequately accounted for varies, making it challenging to isolate the independent effect of T2DM on COVID-19 outcomes. Additionally, the lack of consistent and standardized data on glycemic control among patients limits the ability to determine whether poor glycemic management contributes to worse outcomes or if the risk is primarily driven by diabetes itself. The retrospective nature of many included studies further restricts causal inference, as they are inherently prone to biases such as recall bias and selection bias.

The quality of the studies included in the meta-analysis also presents a limitation. Many studies relied on observational designs, and while efforts were made to include only peer-reviewed research, methodological differences and potential biases in individual studies could impact the overall findings. Publication bias remains a concern, as studies reporting significant associations between T2DM and adverse COVID-19 outcomes may have been more likely to be published than those reporting null or weak associations. This could lead to an overestimation of the risks associated with T2DM. Another challenge is the variation in the definition of"severe"COVID-19 across studies. Some studies categorized severity based on clinical symptoms and hospitalization status, while others used criteria such as ICU admission or specific biomarkers. These discrepancies complicate direct comparisons and may introduce inconsistencies in effect estimates. Furthermore, differences in treatment protocols and medical interventions across countries and time periods may have influenced patient outcomes, making it difficult to draw uniform conclusions.

The exclusion of milder COVID-19 cases in many studies limits the ability to assess the full spectrum of disease severity in individuals with T2DM. Additionally, data on long-term outcomes, including post-COVID complications and recovery trajectories, were scarce, reducing the comprehensiveness of the analysis. Finally, the potential impact of emerging SARS-CoV-2 variants was not fully accounted for in most studies, as new variants with different pathogenic profiles and immune escape potential could alter the relevance of the findings over time. Future research should address these gaps by incorporating prospective studies, standardized definitions of severity, and more detailed data on glycemic control and comorbid conditions to provide a clearer understanding of the relationship between T2DM and COVID-19 outcomes. Additionally, future studies should aim to minimize biases by employing rigorous study designs, ensuring adequate control for confounders, and utilizing standardized methodologies for data collection and outcome assessment.

## Conclusion

The interrelationship between T2DM and COVID-19 outcomes such as mortality, severity and the need for mechanical ventilation is determined by a combination of metabolic dysfunction, chronic inflammation and immune dysregulation. Patients with T2DM are predisposed to severe respiratory and cardiovascular complications when infected with COVID-19, resulting in higher rates of mortality and a higher need for mechanical ventilation. Addressing these risk factors through strict glycemic control and early intervention in diabetic individuals could mitigate the adverse outcomes associated with COVID-19 for this vulnerable population. Further research into the mechanisms of this interrelationship is crucial for improving clinical management and reducing mortality in diabetic patients affected by COVID-19.

### Registration and protocol statement

The current study was registered on PROSPERO with the ID number: CRD42024524007. The review protocol can be accessed via the PROSPERO registry. Subsequently, amendments were made to the information provided at registration. Specifically, the title of the study was revised to the current title, and the number of authors was increased from 4 to 7 to accommodate additional contributors who brought relevant expertise to the study.

**Abbreviations**

| | |
|---|---|
| T2DM | Type 2 Diabetes Mellitus |
| COVID-19 | Coronavirus Disease 2019 |
| SARS-COV 2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| PROSPERO | International Prospective Register of Systematic Reviews |
| ARDS | Acute respiratory Distress Syndrome |

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**Authors' contributions**
BF, ALH, MS, and SOA, DBA Conceptualized and designed the study, conducted data analysis, and contributed to drafting and revising the manuscript. BF, ALH, MS, SOA and DOA Contributed to data collection, interpretation of results, and manuscript review, BF, MS, SOA, ALH, MV, DOA, DBA Participated in study design, data analysis, and critically reviewed the manuscript for important intellectual content. MV, DOA, DBA: Assisted with the literature review, data visualization, and preparation of initial manuscript drafts, All authors provided methodological expertise, oversaw data interpretation, and contributed significantly to manuscript revisions. All authors supported data acquisition and provided feedback on the manuscript drafts. All authors contributed to the manuscript structure, final proofreading, and editing for clarity and coherence; all authors have read and approved the final manuscript.

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**Data availability**
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

**Author details**
[1]General Hospital Lagos, Odan, Lagos Island, Lagos State, Nigeria. [2]Faculty of General Medicine, Siberian State Medical University, Tomsk 634050, Russia. [3]Department of Psychology, National Research Tomsk State University, Tomsk 634050, Russia. [4]National Research Tomsk Polytechnic University, Tomsk 634050, Russia. [5]Global Health and Infectious Disease Control Institute, Nasarawa State University, Keffi, Nasarawa State PMB 1022, Nigeria. [6]Sechenov University, Moscow, Russia. [7]Federal University of Technology, Niger State, Minna, Nigeria.

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