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Afnan Joharji Date. Dec 2, 2021

Morbidity and Mortality among Diabetes Patients Co-infected with COVID-19, by World Health Organization Region, 2020 – 2021

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by
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An abstract submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degreeof Master of Public Health in Hubert Department of Global Health, 2021

Abstract

Morbidity and Mortality among Diabetes Patients Co-infected with COVID-19, by World

Health Organization Region, 2020 – 2021

By Afnan Joharji

Introduction: Corona virus 2019 (COVID-19) is a viral infectious disease caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2). [1] First discovered in Wuhan, China, COVID-19 rapidly spread and was declared a pandemic Feb 11, 2020 by the World Health Organization (WHO). [1] As of Sep 18, 2021 there have been 241,411,380 cases and approximately five million deaths worldwide.[2] Evidence indicates that outcomes from COVID-19 (e.g., acute respiratory syndrome [ARDS], ICU admission, and death) are worse in those with co-morbidities (e.g., hypertension and type-2 diabetes mellites [T2DM]). [3-5] T2DM is a chronic, metabolic, syndrome disorder affecting > 400 million globally. [6],[7] This systematic literature review studied the relationship of T2DM and COVID-19 outcomes (i.e., disease severity and mortality) by WHO region.

Methods: A systematic literature review was performed using PubMed with the following search terms: "COVID-19" OR "SARS-CoV-2" AND "Diabetes" 2) "COVID-19" OR "SARS-CoV-2" AND "Characteristics". Inclusion criteria were in-patients and out-patients with confirmed COVID-19 and T2DM, with the related outcomes (i.e., disease severity, ventilation, ICU admission, ARDS, and death).

Results: This systematic literature review assessed 31 peer-reviewed articles on the relationship between severity and mortality of COVID-19 patients and T2DM by WHO region (i.e., Asia, Middle East, Europe, North America, Latin America) between Feb 1, 2020, and March 31, 2021. People with T2DM were more vulnerable to COVID-19 complications (severe disease or death). The Asia region had the greatest number of studies with high numbers of T2DM prevalence; however, Europe had the highest pooled RR among COVID-19 patients with T2DM and without T2DM.

Conclusion: This systematic review found COVID-19 severity and mortality among patients with T2DM differed by WHO region. This complication may be mitigated by insulin-control. More research is needed in this field to prove whether the outcomes of COVID-19 among T2DM patients differ by WHO region and why.

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Table of Contents

Introduction

Corona virus 2019 (COVID-19) is a viral infectious disease caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2). [1] First discovered in Wuhan, China, COVID-19 rapidly spread and was declared a pandemic Feb 11, 2020 by the World Health Organization (WHO). [1] As of Sep 18, 2021 there have been 241,411,380 cases and approximately five million deaths worldwide.[2]

The prevalence of patients with type-2 diabetes mellites (T2DM) who are co-infected with COVID-19 varies by World Health Organization region. A cross-sectional study from Dubai-United Arab Emirates (UAE) found among 525 hospitalized COVID-19 patients, 177 (34%) also had T2DM. [8] Further, a meta-analysis by Li, *et* al. aimed to describe the epidemiologic and clinical features of COVID-19 patients by reporting the prevalence of chronic diseases (including T2DM); they found 148 of 1,527 (9.7%) hospitalized patients with COVID-19 also had T2DM. In a sub-analysis, T2DM prevalence was 11.7% among ICU or severe patients and 4% among non-ICU or severe patients. [9]

In the United States, a study of 24 patients admitted to the ICU with COVID-19 from nine hospitals in Seattle, Washington found 58% with T2DM. [10] Therefore, while having T2DM does not increase the risk of contracting COVID-19, it can lead to worse outcomes.

Evidence indicates that outcomes from COVID-19 (e.g., acute respiratory syndrome [ARDS], ICU admission, and death) are worse in those with co-morbidities (e.g., hypertension and T2DM). [3-5]

T2DM is a chronic, metabolic, syndrome disorder affecting > 400 million globally. [6]&[7] Currently, one in 11 adults aged 20 – 79 suffers from T2DM. [7] In addition, those with T2DM tend to experience worse outcomes of COVID-19 infection.

A retrospective study conducted from May to July 2020 among 439 hospitalized patients in the Kingdom of Saudi Arabia (KSA) showed how COVID-19 mortality rates differ by T2DM status. [11] The mortality rate was 20.5% among 300 COVID-19 patients with T2DM, and 12.3% among 139 COVID-19 patients without T2DM. Additionally, 58 of 300 COVID-19 patients with T2DM required ICUs; but only 21 of 139 COVID-19 patients without T2DM required ICUs. [11] Another study used data from Massachusetts General Hospital between 11 Mar and 30 Apr 2020 that included 450 hospitalized patients with COVID-19. Among them, 178 patients had T2DM, and 272 patients did not. [12] The mortality rate among T2DM patients with COVID-19 was 15.9% and 8.2% among non-T2DM patients. In addition, the percentage of ICU admission patients was 42.1% among T2DM patients and 29.8 among non-T2DM patients. [12]

The prevalence of T2DM varies by World Health Organization (WHO) region. The T2DM population in Asia accounts for 60% of the global total. [13] Asia has experienced tremendous economic expansion, urbanization, and dietary shifts in recent decades. [14] These factors resulted in a rapid rise in T2DM prevalence in a relatively short period of time. [14] It is also high in urban areas of south India where the prevalence of T2DM reached ~ 20% of the population. [13] For example, a 2-center retrospective study that aimed to describe the characteristics and outcomes of COVID-19 patients with T2DM in China reported that among 1,561 patients, 153 (9.8%) had T2DM. [15] Among them, 17.6% required ICU admission and 20.3% died.

Because T2DM is a major risk factor for COVID-19 complications, it has sparked widespread concern among health professionals and stakeholders (e.g., public health experts and epidemiologists) around the world. However, the relationship between T2DM and COVID-19 outcomes varies by region and is not well understood. **Therefore,** identifying regions with T2DM patients who suffer more from COVID-19 could inform mitigation planning. This systematic literature review examined the relationship between T2DM and COVID-19 outcomes (disease severity and mortality) and assessed geographic regional variance.

Literature Review

Burden of global T2DM

T2DM is a chronic, metabolic disease affecting > 400 million people worldwide. [7] An estimated 3 of 4 people with T2DM reside in low- and middle-income countries (LMICs); the majority remain undiagnosed. [12] The prevalence of T2DM has risen quickly in LMICs over the past 10 years compared with high-income countries (HICs). [16] For example, in a multi-country study of 119,666 participants from three HICs, seven upper-middle-income (UMICs), four LMICs, and four low-income (LICs) countries, the crude prevalence of T2DM differed by country-income group.

Specifically, the age- and sex-adjusted prevalence of T2DM (95% CI) was greatest in LICs (12.3% [95%CI= 10.9% – 13.9%]); followed by UMICs (11.1% [95%CI= 9.7% – 12.6%]); LMICs (8.7% [95%CI= 7.9% – 9.6%]); and HICs (6.6% [95%CI= 5.7% – 7.7%]) (p for trend <0.0001). [16] A pooled analysis among 588,574 participants from 29 LMICs indicated that the overall prevalence of T2DM was 7.5% among adults >25 years old, that increased with income group (LICs 6.7% [95% CI= 5.5 – 8.1]; LMIs 7.1% [95% CI= 6.6 – 7.6]; and UMIs 8.2% [95% CI= 7.5 – 9%]). [12] This study concludes the prevalence of T2DM was greater in both LICs and UMICs compared with HICs. [17]

There are several factors that contribute to the higher prevalence of T2DM in LMICs (e.g., income, age, region, and disease severity). [18, 19] Risk factors behind regional differences in the prevalence of T2DM also vary. First, age is a risk factor for T2DM. A study conducted in a suburban district of Sri Lanka – a LIC – aimed to assess the inequalities of T2DM and risk factors. [20] It reported 202 of 1,234 adults had T2DM; they found persons 55 – 59 years old had the highest prevalence of T2DM (23.4%) compared to persons 35 – 39 years old with a prevalence of 4.8%. [20]

However, many countries with high T2DM prevalence have lower age structures. For example, in New Zealand, the group ≥ 65 years old have the greatest prevalence of T2DM – 15% – 20%. The Ministry of Health's Virtual Diabetes Register in New Zealand showed T2DM prevalence in people aged 25 – 39 years nearly doubled between 2006 and 2018. [21]

Second, LMICs often have a greater prevalence of undiagnosed diabetes. A study aimed to describe the prevalence and risk factors of undiagnosed diabetes in rural Bangladesh reported that from 7.2% of 3,104 adults ≥ 30 years old had T2DM and 55% were undiagnosed; most were of lower socioeconomic status (59%). [22] In terms of age-adjusted prevalence, the Middle East and North Africa (MENA) had the highest prevalence of T2DM in 2019 (12.2%), while Africa had the lowest prevalence (4.7%). [23]

While evidence indicates the prevalence of T2DM is high in LMICs (and we do know risk factors that contribute) there is a need for evidence of COVID-19 severity and mortality among diabetic patients, by WHO region.

Prevalence of T2DM among COVID-19 cases

Several studies examine the prevalence of T2DM among individuals with COVID-19; these vary widely. A meta-analysis of 23 studies (including 49,564 patients) evaluated the prevalence of T2DM among COVID-19 patients from Dec 1, 2019 to Mar 31, 2020 in China. [24] They found the prevalence of T2DM ranged from 2.47% - 22.22% and the pooled prevalence of T2DM was 10% (95%

CI= 7% - 15%). This was slightly greater than the estimated prevalence of 8.5% in the general population. [24] Another meta-analysis of seven studies included 1,576 hospitalized patients with COVID-19 and aimed to assess the prevalence of comorbidities. They reported a T2DM prevalence of 9.7%. [5]

Additionally, a meta-analysis of 10 studies comprising 76,993 hospitalized COVID-19 patients aimed to estimate the prevalence of underlying diseases – including T2DM – and reported that among COVID-19 patients, the prevalence of T2DM was 7.87% (95% CI= 6.57% - 9.28%). [25] Further, a meta-analysis of 10 studies from China that included 2,209 hospitalized COVID-19 patients described the prevalence of comorbidities among COVID-19 patients. It reported that the pooled prevalence of T2DM was 11%; the prevalence for each study varied from 7.4% - 19.5%. [26] Moreover, a small study conducted between Feb 24, 2020 and Mar 9, 2020 reviewed comorbidities among COVID-19 patients admitted to the ICU from nine hospitals in the state of Washington (United States); they found the prevalence of T2DM to be 58%. [10]

Evidence indicates that among patients hospitalized with COVID-19, the prevalence of T2DM ranged from 7.87% - 11%; this is similar to that of the general population. However, a study by Bhatraju PK, *et* al. 2020 conducted in the United States reported a much higher prevalence of T2DM (58%). [10] This could be affected by other factors such as a small sample size (24 patients) and mean age of 64 years. Further, all patients in the study were admitted to the ICU that may lead to an inflated prevalence and suggest that T2DM may link to COVID-19 severity. This suggests that T2DM does not increase the risk of COVID-19 since the prevalence does not appear to be greater than in the general population. [27] However, COVID-19 patients with preexisting diabetes may be at increased risk for severe disease or disease outcomes.

Mechanism linking T2DM to COVID-19

T2DM has been associated with increased risk for infectious diseases. [28] Evidence suggests there is a mechanistic link between T2DM and COVID-19 that may result in adverse clinical outcomes. T2DM could have a harmful impact on the disease pathway through its effect on the receptors that mediate virus entry into the cell. COVID-19 receptor proteins include the angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase-4 (DPP4) both of which have roles in organizing several physiological processes, including glucose metabolism. They are modified by hyperglycemia and common treatments used in people with T2DM. [29]

It has been suggested that a link exists between SARS-CoV-2 and ACE2, whereby the former decreases the expression or the activity of this receptor and promotes the vasoconstrictor and pro-inflammatory/pro-oxidant activity of angiotensin II thus increasing blood pressure by a variety of mechanisms. The most important being vasoconstriction, sympathetic nervous stimulation, enhanced aldosterone biosynthesis, and renal actions. [30] This raises the risk for acute lung injury due to the increased concentration of angiotensin II that lead to releasing of cytokines, chemokines, and ROS; thus exacerbate the lung damage. [31]

But RAS blockers may assist in reducing these harmful impacts of angiotensin II. [32] In addition to RAS activation, T2DM and other comorbidities are also linked with elevated levels of plasmin (ogen), a protease that splits the S-protein of SARS-CoV2, which may enable the virus to link to ACE2 and enter into the cell; furthermore, fibrin breakdown, which is a fibrous, non-globular protein that plays a role in blood coagulation, by plasmin levels to high levels of D-dimer and other fibrin degradation products, which are special features of severe disease such as acute venous thromboembolism, ischemic cardiovascular disease and cancer. [33, 34] T2DM has long been known as a risk factor for infection-related morbidity and mortality, especially infections caused by respiratory viruses. [35]

Severity and mortality outcomes related to T2DM

Evidence indicates that T2DM is linked with worse COVID-19 complications and increased disease severity and mortality. A study of 138 hospitalized COVID-19 patients reported that 46.4% had one or more underlying conditions. The prevalence of T2DM in the overall population was 10.1%; however, it was 22.2% among the 36 patients who were in the ICU. [3] Another study conducted in China among 201 COVID-19 patients $\geq$ 42 years old reported 84 (41.8%) developed acute respiratory distress syndrome (ARDS). The mortality rate of those with ARDS was 52.4% [3]; those who had T2DM were at increased risk (RR=2.34;95% CI=1.35 - 4.05; p=0.002) for ARDS. [36] In a study from Massachusetts General Hospital in the United States of 450 patients hospitalized with COVID-19, compared to those without T2DM among those with T2DM, a greater proportion were admitted to the ICU (42.1% vs. 29.8%, respectively; P = 0.007), required mechanical ventilation (37.1% vs. 23.2%; p= 0.001), and died (15.9% vs. 7.9%;p= 0.009). [12] Furthermore, the Italian National Institute of Health reported the prevalence of T2DM among 355 patients who died while infected with COVID-19 to be 35.5%; however, the estimated prevalence of T2DM among the general population is 20.3%. [37]

One study aimed to compare epidemiologic characteristics and outcomes of COVID-19 in patients with T2DM versus patients without T2DM. [38] Of 16,391 participants, 8.3% had T2DM and 28.3% of COVID-related mortality among diabetic patients. [38] The mortality rate among 1,365 diabetic patients was 14.4% compared to 3.3% of 15,026 non-diabetic patients. [38] Another study conducted of 108 COVID-19 hospitalized patients at the Cheikh Khalifa Al Nahyan Hospital between Mar 20 and May 1, 2020 showed the mortality rate among 25 diabetic patients was 16% compared to 9.3% among 108 non-diabetic patients. [39] These results indicate there is a relationship between T2DM and increased risk of disease severity and mortality among COVID-19 patients. Research also indicates that COVID-19 complications (e.g., pneumonia, ventilation, ICU admission, and mortality) are worse in individuals whose T2DM is not well controlled. [40]

For example, a cohort study conducted in Britain among 17 million adults from Feb 1, 2020 to Apr 25, 2020 found that of the 5,693 COVID-19 in-hospital deaths, patients with uncontrolled T2DM were at greater risk of death (RR= 2.36; 95%CI= 2.18-2.56) compared to controlled T2DM (RR=1.50; 95%CI= 1.40-1.60). [41] While T2DM is linked to worse COVID-19 outcomes, there is little known whether COVID-19 outcomes might differ by WHO region. This systematic review will investigate whether COVID-19 severity and mortality vary among patients with T2DM in various WHO regions.

Summary of current problem and study relevance

Globally, research addresses the relationship between COVID-19 severity and mortality with the presence of comorbidities, including T2DM. Many studies focus on one country or region. Some are global but these do not focus on comparing COVID-19 outcomes among T2DM patients by WHO region. This systematic review addresses the gap regarding potential WHO regional variability in COVID-19 outcomes and T2DM by identifying regions that are hardest hit by the COVID-19 pandemic.

Methods

Search strategy and study selection

A systematic literature search was performed in PubMed with the following search terms: "COVID-19" OR "SARS-CoV-2" AND "Diabetes" 2) "COVID-19" OR "SARS-CoV-2" AND "Characteristics". The results were filtered for the following: English; MEDLINE; free full text; and article type (i.e., clinical trial, observational, randomized clinical trial). Initially, 452 articles in the English language were found; 450 records remained after duplicates using EndNote X9 and the remaining articles were screened for relevance by the title in EndNote X9. After removing the irrelevant titles, another independently screening had done for the remaining study abstracts in PubMed. Three hundred articles were excluded from 450 after abstract review. All articles were assessed according to the inclusion and exclusion criteria. After 150 full-text articles were assessed for suitability, 119 omissions of full-text articles were made because there was no outcome of interest since they had to have T2DM numbers for cases and controls, so we could calculate the risk ratio; otherwise, they were excluded. We included the remaining 31 full-text studies.

Eligibility criteria

Inclusion criteria were in- and out-patients with confirmed COVID-19 and T2DM, with the related outcomes (i.e., disease severity, ventilation, ICU admission, ARDS, and death). Eligible articles were published between Feb 1, 2020, and Mar 31, 2021 with certain type of studies. Articles that were not original research (i.e., letters, agency reports), had a sample size < 20, published in languages other than English, didn’t have the required data (i.e., number of deaths among diabetic and nondiabetic patients) plus articles focusing on children were excluded.

Statistical analysis

OpenEpi was used in this systematic review to establish the risk ratio and 95% confidence interval by entering the needed numbers in a 2 X 2 table. The disease cells stand for the outcome (mortality or severity), and the exposure cells stand for T2DM.

Results

This systematic literature review assessed 31 peer-reviewed articles on the relationship between severity and mortality of COVID-19 patients and T2DM, by WHO region. [39, 42-71] Details included their geographic location, sample size, study population, male percentage, mean or median age, and the prevalence of T2DM were reported, by study (Table 1). Among the studies, the sample size varied greatly and ranged from 52 [71] to 23,844 participants. [60] The range of T2DM prevalence – the lowest reported was 1.7% [68] and highest was 89.2% [59] were both in the WHO Asia region. Most COVID-19 cases (with co-morbid T2DM) were among those > 40 years of age. The included studies assessed a mortality outcome or a severity of disease outcome in relation to T2DM. The number reporting mortality were 17, where 12 studies reported severity of disease; two include both severity and mortality. Fourteen studies from the Asia region (China, India, and South Korea) were included. The prevalence of diabetes among COVID-19 patients ranged from 1.7% to 89.2%. [59] [68] Among the 14 studies from Asia, nine assessed severe disease outcomes, four mortality outcomes, and one study both mortality and severe disease outcomes.

Table 1. Demographic Characteristics of COVID-19 Patients with T2DM, by WHO Asia Region, 2019 – 2020

Reference [1]	**Asia Region Country**	**Sample Size**	**Male (%)**	**Age** [2 or 3]	**Diabetes (%)**	**Outcomes**[4 or 5]
[45]	China	720	62	74 [c]	11.8	d
[46]	China	145	54.5	47.5 [b]	9.7	d
[51]	China	397	52	50 [c]	10	d
[55]	South Korea	110	43.6	57 [b]	26.4	d
[56]	South Korea	1,082	45.1	68.3 [b]	21.7	d & e
[59]	China	1,880	48	63 [b]	89.2	d
[61]	India	401	74.6	54 [c]	47	d
[65]	China	129	48.1	50 [c]	12.4	d
[66]	China	3,400	48.5	61 [c]	21.6	e
[67]	China	74	71.6	68 [c]	63.5	e
[68]	China	6,269	51.2	64 [c]	1.7	e
[69]	China	116	69	58.5 [c]	16.4	d
[70]	China	193	59.1	64 [c]	24.9	e
[71]	China	52	63.5	65.5 [c]	42.3	d

1 All studies listed were observational

2 mean

3 median

4 severe disease

5 mortality

Three studies from the Middle East region (Iran, Morocco, and Dubai) were included. (Table 2) The prevalence of diabetes among COVID-19 patients ranged from 18.7% in Morocco to 29.4% in Iran.

Table 2. Demographic Characteristics of COVID-19 Patients with T2DM, by WHO Middle East Region, 2019 – 2020

Reference [a]	**Middle East Region Country**	**Sample Size**	**Male (%)**	**Age [b or c]**	**Diabetes (%)**	**Outcomes d [or] e**
[39]	Morocco	133	54.9	53 [c]	18.7	e
[42]	Iran	595	67.4	55 [c]	29.4	d & e
[44]	Dubai	410	66.9	54 [b]	25.1	e

a All studies listed were observational

b mean

c median

d severe disease

e mortality

Moreover, in Europe, the prevalence of T2DM from three studies in Italy was 11.4%, 12.8%; and 15%. (Table 3) Two studies in the UK revealed 22.5% and 30.2%. Three studies were in Spain 21.8%; 8.8%; 24.30%. One study in Germany reported the prevalence of T2DMN to be 15.2. One study in Greece reported the prevalence of T2DM to be 18.9%.

Table 3: Demographic Characteristics of COVID-19 Patients with T2DM, by WHO Europe Region, 2019 – 2020

Reference [a]	**Europe Region Country**	**Sample Size**	**Male (%)**	**Age** [b or c]	**Diabetes (%)**	**Outcome** [d or e]
[43]	Spain	4,035	61	70 [c]	21.8	[e]
[47]	United Kingdom	215	62%	74 [c]	30.2	[e]
[48]	Italy	410	72.9	65 [c]	15	[e]
[49]	United Kingdom	71	NA	70.5 [c]	22.5	[e]
[50]	Italy	195	66.5	57 [b]	11.4	[d]
[52]	Spain	742	68	64 [b]	24.3	[d]
[53]	Italy	3,988	79.9	63 [c]	12.8	[e]
[54]	Greece	90	80	65.5 [c]	18.9	[e]
[60]	Spain	23,844	42.3	49.93 [b]	8.8	[e]
[63]	Germany	1904	51.5	73 [c]	15.2	[e]

a Study 49 was a clinical trial and study 63 was a retrospective cohort study. All other studies in the table were observational.

b mean

c median

d severe disease

e mortality

In North American, three studies were conducted in the United States of America that reported the prevalence of T2DM 38.8%; 45.7% and 65%; all related to mortality. (Table 4)

Table 4: Demographic Characteristics of COVID-19 Patients with T2DM, by WHO North America Region, 2019 – 2020

Reference [a]	**North America Region Country**	**Sample Size**	**Male (%)**	**Age** [b or c]	**Diabetes (%)**	**Outcome** [d or e]
[57]	USA	85	67	60 [b]	38.8	[e]
[58]	USA	152	62.5	68 [c]	65	[e]
[62]	USA	81	69.1	64 [c]	45.7	[e]

a studies 57 and 58 are observational and study 62 is retrospective observational cohort study.

b mean

c median

d severe disease

e mortality

In the WHO South America region one study related to mortality in Mexico with the prevalence of T2DM of 32.3%. (Table 5)

Table 5: Demographic Characteristics of COVID-19 Patients with T2DM, by WHO Latin America Region, 2019 – 2020

Reference [a]	**Latin America Region Country**	**Sample Size**	**Males (%)**	**Age** [b or c]	**Diabetes (%)**	**Outcome** [d or e]
[64]	Mexico	164	69.5	57.3 [b]	32.3	[e]

a all studies are observational

b mean

c median

d severe disease

e mortality

Results from these studies found patients with T2DM were more vulnerable to coronavirus complications (severity and mortality). (Table 6) Twenty studies assessed mortality due to COVID-19 among patients with T2DM in all WHO regions with pooled RR of 2.54 (95%CI=2.41-2.68). Five pooled studies from Asia had a RR=2.52 (95% CI= 2.19-2.91); three from Middle East had a RR=1.4 (95%CI= 0.92-2.11); eight from Europe had a RR= 2.53 (95%CI= 2.38-2.68); three studies from North America had a RR= 1.02 (95% CI= 0.80-1.30). One study from Latin America had a RR=1.76 (95%CI= 1.33-2.33).

Table 6. T2DM and Poor Outcomes, by WHO Region, 2019 – 2020

Reference	Diabetes mellitus (+)		Diabetes mellitus (-)		Risk ratio (95% CI)
	Events	Total	Events	Total	
1.1 Mortality due to COVID-19					
Asia region					
[56]	44	235	41	847	3.87 (2.59- 5.77)
[66]	46	733	27	2,667	6.20 (3.88- 9.90)
[67]	2	14	48	60	0.18 (0.05- 0.65)
[68]	73	126	576	7,157	7.20 (6.09- 8.52)
[70]	39	48	69	145	1.71 (1.37- 2.12)
Pooled risk ratio (95%CI)	204	1,156	761	10,876	2.52 (2.19- 2.91)
Middle East region					
[42]	26	148	39	447	2.02(1.27- 3.19)
[39]	4	25	10	108	1.73(0.59- 5.06)
[44]	3	90	2	13	0.22 (0.04, 1.18)
Pooled risk ratio (95%CI)	33	263	51	568	1.4 (0.92- 2.11)
Europe region					
[47]	23	65	63	150	0.84 (0.58- 1.23)
[48]	1	61	19	337	0.29 (0.04- 2.132)
[49]	4	16	19	55	0.72 (0.29- 1.82)
[53]	328	514	1598	3474	1.39 (1.29- 1.49)
[54]	8	17	18	73	1.91(1.00- 3.64)
[63]	57	258	260	1,577	1.34(1.04- 1.73)
[60]	278	2101	577	21743	4.99 (4.35-5.71)
[43]	375	889	756	3131	1.75 (1.58- 1.93)
Pooled risk ratio (95%CI)	1,074	3,921	3,310	30,540	2.53 (2.38- 2.68)
North America region					
[57]	8	33	12	52	1.051 (0.48- 2.29)
[58]	43	69	49	83	1.056 (0.82- 1.36)
[62]	14	37	21	44	0.79 (0.47- 1.33)
Pooled risk ratio (95%CI)	65	139	82	179	1.02 (0.80- 1.30)
Latin America region					
[64]	37	53	48	121	1.76 (1.33- 2.33)
Subtotal (95%CI)		5,532		42,284	2.54 (2.41- 2.68)
Total events	1,413		4,252		

Additionally, there were 15 studies from all regions that assessed disease severity and had a pooled RR of 1.71 (95%CI=1.54-1.9). Among them, 12 were from Asia with a pooled RR of 1.62 (95% CI=1.44-1.82); three from Europe had a pooled RR of 1.73 (95%CI=1.40-2.14). (Table 7)

Table 7. T2DM and Poor Outcomes, by WHO Region, 2019 – 2020

Reference	**Diabetes mellitus (+)**		**Diabetes mellitus (-)**		**Risk ratio (95% CI)**
	Events	**Total**	**Events**	**Total**	
1.2 Severe COVID-19					
		Asia region			
[45]	12	119	31	888	2.89 (1.53- 5.47)
[46]	7	14	36	131	1.82 (1.01- 3.29)
[51]	2	11	9	337	6.81 (1.66- 27.87)
[55]	14	29	9	81	4.35 (2.11- 8.94)
[56]	65	235	94	847	2.49 (1.88- 3.30)
[59]	53	139	235	795	1.29 (1.02- 1.64)
[65]	7	16	33	113	1.50 (0.80- 2.80)
[69]	11	19	44	147	1.93 (1.23- 3.05)
[71]	11	22	10	30	1.5 (0.78- 2.89)
[66]	72	733	224	2594	1.14 (0.88- 1.46)
[70]	32	48	60	145	1.61 (1.22- 2.13)
[61]	38	189	19	212	2.24 (1.34- 3.75)
Pooled risk ratio (95%CI)	324	1,574	804	6,320	1.62 (1.44- 1.82)
		Europe region			
[50]	17	21	105	174	1.34 (1.06- 1.71)
[52]	76	180	207	562	1.146 (0.94- 1.40)
[53]	2	514	12	3,474	1.126 (0.25- 5.02)
Pooled risk ratio (95%CI)	95	715	324	4,210	1.73 (1.40- 2.14)
Subtotal (95%CI)		2,289		10,530	1.71 (1.54- 1.90)
Total events	419		1,128		

The findings of this systematic review suggested that the relationship between T2DM and COVID-19 severity and mortality differ by WHO region. Among 31 studies, the WHO Europe region – ten studies – had a statistically significant effect between diabetes and COVID-19 outcomes (either severe disease or mortality). T2DM was significantly associated with mortality linked to COVID-19 with a pooled risk ratio of 2.54 (95% CI=2.41-2.68). In addition, T2DM was associated with severe COVID-19, including risk of ARDS, ICU admission, and invasive ventilatory requirement, with a pooled risk ratio of 1.71 (95%CI=1.54-1.9).

The WHO Asia region had the greatest number of studies (14); nine related to severe disease, four to mortality, and one to both severity and mortality. Four of these had RRs > 4 (RR=6.81; 95% CI= 1.66,27.87) [51]; (RR= 7.2; 95% CI= 6.09,8.52) [68]; (RR= 4.35; 95% CI= 2.11,8.94) [55]; and (RR= 6.2; 95% CI= 3.88, 9.89). [66] One study reported the greatest prevalence of T2DM of 89.2% (RR= 1.29; 95% CI= 1.02-1.64) related to severe disease. [59]

The WHO Middle East region included three studies. One assessed severity and mortality and two assessed mortality. All risk ratios were between 0 and two. The prevalence of T2DM begins from 18% to 29.4%. One had the greatest prevalence at 29.4% and the highest RR= 2.01; 95 CI%= 1.27-3.19). [42]

The WHO Europe region included ten studies (Italy, UK, Spain, Germany, and Greece). Two assessed disease severity, and eight assessed mortality. The prevalence of T2DM in the UK (22.5% and 30.2%) tended to be greater than in Italy (11.4%, 12.8%, and 15%) and Germany (15.2%). However, the RRs were < 1. Additionally, the median age ranged from 70.5 to 74 years old. Two studies from Italy had a RR >1 (1.34, 95%CI=1.06-1.71) (1.39, 95% CI=1.29-1.49). [50] [53]. One study in Europe assessed mortality and had the lowest prevalence of T2DM (8.8%). However, it has the highest RR of 4.99 (95% CI= 4.35-5.71).

North America included three studies; all assessed mortality. The prevalence of T2DM ranged from 38.8% to 65%. One study had the greatest prevalence of T2DM at 65% (RR=1.06; 95% CI= 0.82-1.36). [58] In general, the relationship between T2DM and COVID-19 outcome is not statistically significant in North America. One study conducted in Mexico assessed mortality and reported the prevalence of T2DM 32.3% and RR=1.76 (95%CI=1.33-2.33).

Table 6 and 7 described COVID-19 severity and mortality by T2DM status. Among studies that related to mortality, the total number of diabetic patients among all regions was 5,532 with 1,413 deaths. However, there were 4,252 deaths out of 42,284 COVID-19 patients without T2DM, with pooled RR= 2.54 (95%CI=2.41-2.68). There were 545 deaths among 8,715 COVID-19 patients with T2DM, and 1,148 deaths among 11,369 COVID-19 patients without T2DM.

Discussion

Summary of evidence

T2DM among COVID-19 patients contributed to poorer outcomes (severity and mortality). The characteristics of COVID-19 patients with T2DM varied by WHO region (Asia, Middle East, Europe, North America, and Latin America). While the number of studies in each region was not equal, Asia had the greatest number (14). Latin America has the smallest number (one). This could affect the strength of this review. Asia had a high prevalence (42.3%, 47%, 63.5%, and 89.2%) compared to North America which had three studies and T2DM prevalence of 38.8%, 45.7%, 65%. The review showed that among four meta-analyses conducted globally, the prevalence of T2DM among COVID-19 patients ranged from 7.87% - 11%. [5], [24-26] which was lower than the studies in the systematic review.

The number of deaths/cases with severe disease among COVID-19 patients with T2DM and the number of death/cases with severe disease among COVID-19 without T2DM varied by WHO region. Among mortality oucome, Asia and Europe regions have the highest pooled RR 2.52 (2.19- 2.91) and 2.53 (2.38- 2.68), respectively. However, among severe COVID-19 patients, the pooled RR of Europe region 1.71 (1.54- 1.90) higher than Asia region 1.62 (1.44- 1.82). In general, the risk of mortality among COVID-19 patients with T2DM was > twice the risk of mortality among COVID-19 patients without T2DM. However, the risk of severe disease among COVID-19 patients with T2DM was 1.71 times the risk among COVID-19 patients without T2DM. We can infer that the risk of mortality was greater than the risk of disease severity. Several studies from this systematic literature review established that T2DM had an impact on COVID-19 severity and mortality. [3], [12], [36], [39]

Limitations

Research addressing whether COVID-19 severity and mortality may differ by WHO region was limited, making this systematic review one of the first studies that aimed to investigate this point by including studies from five regions (Asia, Middle East, Europe, North America, and Latin America). This review included a large number of studies (31) with 52,082 patients; however, it did not include studies from Africa. Plus, the number of studies in each region is not equal; Asia had the greatest number (14). Moreover, the research were limited with filters that mitigated the number of studies. Finally, a meta- analysis would make this systematic review stronger by showing more statistics.

Conclusion

This systematic review found that COVID-19 severity and mortality among patients with T2DM differed by WHO region. People with T2DM were more vulnerable for COVID-19 complications. Asia had the greatest number of studies with high T2DM prevalence; however, Europe had the highest pooled RR among COVID-19 patients with T2DM and without T2DM. This complications may be mitigated by insulin-control. More research is needed in this field to prove whether the outcomes of COVID-19 among T2DM patients differ by WHO region.

Public health implications

The experience of COVID-19 in healthcare setting has significant implications for public health globally. This pandemic has revealed which countries have the strongest public health systems.

Recommendations

First of all, further research should include studies from Africa with more for each region to be more supported whether COVID-19 severity and mortality among T2DM patients differ by WHO regions. Second, a meta-analysis is recommended for further details such as the pooled prevalence of T2DM for each region. Finally, Education regarding insulin- control is needed for T2DM patients since this is a critical point on their health as well as encouragement to take all the shots of COVID-19 vaccine to mitigate the complications.

References

1. Lai, C.C., et al., *Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges.* International Journal of Antimicrobial Agents, 2020.
2. Organization, W.H. *WHO Coronavirus (COVID-19) Dashboard*. 2021.
3. Wang, D., et al., *Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China.* JAMA, 2020. **323**(11): p. 1061-1069.
4. Sanyaolu, A., et al., *Comorbidity and its Impact on Patients with COVID-19.* SN Compr Clin Med, 2020: p. 1-8.
5. Yang, J.-K., et al., *Blood glucose is a representative of the clustered indicators of multi-organ injury for predicting mortality of COVID-19 in Wuhan, China*. medRxiv, 2020: p. 2020.04.08.20058040.
6. Organization, W.H., *Diabetes.* 2021.
7. Federation, I.D., *Diabetes Facts & figures.* Diabetes Atlas, 2020.
8. Hannawi, S., et al., *Clinical and Laboratory Profile of Hospitalized Symptomatic COVID-19 Patients: Case Series Study From the First COVID-19 Center in the UAE.* Front Cell Infect Microbiol, 2021. **11**: p. 632965.
9. Li, B., et al., *Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China.* Clin Res Cardiol, 2020. **109**(5): p. 531-538.
10. Bhatraju, P.K., et al., *Covid-19 in Critically Ill Patients in the Seattle Region - Case Series.* N Engl J Med, 2020. **382**(21): p. 2012-2022.
11. Alguwaihes, A.M., et al., *Diabetes and Covid-19 among hospitalized patients in Saudi Arabia: a single-centre retrospective study*. Cardiovascular Diabetology, 2020. **19**(1): p. 205.
12. Seiglie, J.A., et al., *Diabetes Prevalence and Its Relationship With Education, Wealth, and BMI in 29 Low- and Middle-Income Countries.* Diabetes care, 2020. **43**(4): p. 767-775.
13. Hu, F.B., *Globalization of Diabetes.* The role of diet, lifestyle, and genes, 2011. **34**(6): p. 1249-1257.
14. Chan, J.C., et al., *Diabetes in Asia: epidemiology, risk factors, and pathophysiology*. Jama, 2009. **301**(20): p. 2129-40.
15. Shi, Q., et al., *Clinical Characteristics and Risk Factors for Mortality of COVID-19 Patients With Diabetes in Wuhan, China: A Two-Center, Retrospective Study*. Diabetes Care, 2020. **43**(7): p. 1382-1391.
16. Dagenais, G.R., et al., *Variations in Diabetes Prevalence in Low-, Middle-, and High-Income Countries: Results From the Prospective Urban and Rural Epidemiological Study*. Diabetes Care, 2016. **39**(5): p. 780-7.
17. Cho, N.H., et al., *IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045.* Diabetes Res Clin Pract, 2018. **138**: p. 271-281.
18. Danaei, G., et al., *National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants.* Lancet, 2011. **378**(9785): p. 31-40.
19. Corsi, D.J. and S.V. Subramanian, *Association between socioeconomic status and self-reported diabetes in India: a cross-sectional multilevel analysis.* BMJ Open, 2012. **2**(4).

20. De Silva, A.P., et al., *Inequalities in the prevalence of diabetes mellitus and its risk factors in Sri Lanka: a lower middle income country.* Int J Equity Health, 2018. **17**(1): p. 45.
21. medicine, b. *A rising tide of type 2 diabetes in younger people: what can primary care do?* 2021; Available from: https://bpac.org.nz/2021/diabetes-younger.aspx.
22. Islam, F.M.A., et al., *Prediabetes, diagnosed and undiagnosed diabetes, their risk factors and association with knowledge of diabetes in rural Bangladesh: The Bangladesh Population-based Diabetes and Eye Study.* Journal of Diabetes, 2016. **8**(2): p. 260-268.
23. Atlas, I.D. *Demographic and geographic outline*. 2019; Available from: https://diabetesatlas.org/en/sections/demographic-and-geographic-outline.html.
24. Du, M., et al., *Prevalence and impact of diabetes in patients with COVID-19 in China.* World J Diabetes, 2020. **11**(10): p. 468-480.
25. Emami, A., et al., *Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis.* Arch Acad Emerg Med, 2020. **8**(1): p. e35.
26. Singh, A.K., R. Gupta, and A. Misra, *Comorbidities in COVID-19: Outcomes in hypertensive cohort and controversies with renin angiotensin system blockers.* Diabetes Metab Syndr, 2020. **14**(4): p. 283-287.
27. Association, A.D. *How COVID-19 Impacts People with Diabetes*. 2021; Available from: https://www.diabetes.org/coronavirus-covid-19/how-coronavirus-impacts-people-with-diabetes.
28. Kim, E.J., et al., *Diabetes and the Risk of Infection: A National Cohort Study.* Diabetes Metab J, 2019. **43**(6): p. 804-814.
29. Drucker, D.J., *Coronavirus Infections and Type 2 Diabetes-Shared Pathways with Therapeutic Implications.* Endocr Rev, 2020. **41**(3).
30. Fyhrquist, F., K. Metsärinne, and I. Tikkanen, *Role of angiotensin II in blood pressure regulation and in the pathophysiology of cardiovascular disorders.* J Hum Hypertens, 1995. **9 Suppl 5**: p. S19-24.
31. Gao, Y.L., et al., *Role of Renin-Angiotensin System in Acute Lung Injury Caused by Viral Infection.* Infect Drug Resist, 2020. **13**: p. 3715-3725.
32. Zhang, P., et al., *Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19.* Circ Res, 2020. **126**(12): p. 1671-1681.
33. Ji, H.L., et al., *Elevated Plasmin(ogen) as a Common Risk Factor for COVID-19 Susceptibility.* Physiol Rev, 2020. **100**(3): p. 1065-1075.
34. Di Castelnuovo, A., et al., *Association of D-dimer levels with all-cause mortality in a healthy adult population: findings from the MOLI-SANI study.* Haematologica, 2013. **98**(9): p. 1476-1480.
35. Pugliese, G., et al., *Is diabetes mellitus a risk factor for COronaVIrus Disease 19 (COVID-19)?* Acta Diabetol, 2020. **57**(11): p. 1275-1285.
36. Wu, C., et al., *Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China.* JAMA Intern Med, 2020. **180**(7): p. 934-943.

37. Fleming, N., et al., *An overview of COVID-19 in people with diabetes: Pathophysiology and considerations in the inpatient setting.* Diabet Med, 2021. **38**(3): p. e14509.
38. Moftakhar, L., et al., *Epidemiological characteristics and outcomes of COVID-19 in diabetic versus non-diabetic patients.* Int J Diabetes Dev Ctries, 2021: p. 1-6.
39. Elamari, S., et al., *Characteristics and outcomes of diabetic patients infected by the SARS-CoV-2.* Pan Afr Med J, 2020. **37**: p. 32.
40. Apicella, M., et al., *COVID-19 in people with diabetes: understanding the reasons for worse outcomes.* Lancet Diabetes Endocrinol, 2020. **8**(9): p. 782-792.
41. Williamson, E.J., et al., *Factors associated with COVID-19-related death using OpenSAFELY.* Nature, 2020. **584**(7821): p. 430-436.
42. Akbariqomi, M., et al., *Clinical characteristics and outcome of hospitalized COVID-19 patients with diabetes: A single-center, retrospective study in Iran.* Diabetes Res Clin Pract, 2020. **169**: p. 108467.
43. Berenguer, J., et al., *Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain.* Clin Microbiol Infect, 2020. **26**(11): p. 1525-1536.
44. Bhatti, R., et al., *Clinical Characteristics and Outcomes of Patients With Diabetes Admitted for COVID-19 Treatment in Dubai: Single-Centre Cross-Sectional Study.* JMIR Public Health Surveill, 2020. **6**(4): p. e22471.
45. Cen, Y., et al., *Risk factors for disease progression in patients with mild to moderate coronavirus disease 2019-a multi-centre observational study.* Clin Microbiol Infect, 2020. **26**(9): p. 1242-1247.
46. Chen, Q., et al., *Clinical characteristics of 145 patients with corona virus disease 2019 (COVID-19) in Taizhou, Zhejiang, China.* Infection, 2020. **48**(4): p. 543-551.
47. Chinnadurai, R., et al., *Older age and frailty are the chief predictors of mortality in COVID-19 patients admitted to an acute medical unit in a secondary care setting- a cohort study.* BMC Geriatr, 2020. **20**(1): p. 409.
48. Ciceri, F., et al., *Early predictors of clinical outcomes of COVID-19 outbreak in Milan, Italy.* Clin Immunol, 2020. **217**: p. 108509.
49. Conway, J., et al., *Characteristics of patients with diabetes hospitalised for COVID-19 infection-a brief case series report.* Diabetes Res Clin Pract, 2020. **169**: p. 108460.
50. De Lorenzo, R., et al., *Residual clinical damage after COVID-19: A retrospective and prospective observational cohort study.* PLoS One, 2020. **15**(10): p. e0239570.
51. Duan, J., et al., *Correlation between the variables collected at admission and progression to severe cases during hospitalization among patients with COVID-19 in Chongqing.* J Med Virol, 2020. **92**(11): p. 2616-2622.
52. Ferrando, C., et al., *Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS.* Intensive Care Med, 2020. **46**(12): p. 2200-2211.
53. Grasselli, G., et al., *Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy.* JAMA Intern Med, 2020. **180**(10): p. 1345-1355.
54. Halvatsiotis, P., et al., *Demographic and clinical features of critically ill patients with COVID-19 in Greece: The burden of diabetes and obesity.* Diabetes Res Clin Pract, 2020. **166**: p. 108331.

55. Jang, J.G., et al., *Prognostic Factors for Severe Coronavirus Disease 2019 in Daegu, Korea.* J Korean Med Sci, 2020. **35**(23): p. e209.
56. Kim, M.K., et al., *The Clinical Characteristics and Outcomes of Patients with Moderate-to-Severe Coronavirus Disease 2019 Infection and Diabetes in Daegu, South Korea.* Diabetes Metab J, 2020. **44**(4): p. 602-613.
57. Krause, M., et al., *Characteristics and Outcomes of Mechanically Ventilated COVID-19 Patients—An Observational Cohort Study.* Journal of Intensive Care Medicine, 2021. **36**(3): p. 271-276.
58. Krishnan, S., et al., *Clinical comorbidities, characteristics, and outcomes of mechanically ventilated patients in the State of Michigan with SARS-CoV-2 pneumonia.* J Clin Anesth, 2020. **67**: p. 110005.
59. Liu, Z., et al., *Association Between Diabetes and COVID-19: A Retrospective Observational Study With a Large Sample of 1,880 Cases in Leishenshan Hospital, Wuhan.* Front Endocrinol (Lausanne), 2020. **11**: p. 478.
60. Mayer, M.A., et al., *Clinical Characterization of Patients With COVID-19 in Primary Care in Catalonia: Retrospective Observational Study.* JMIR Public Health Surveill, 2021. **7**(2): p. e25452.
61. Mithal, A., et al., *High prevalence of diabetes and other comorbidities in hospitalized patients with COVID-19 in Delhi, India, and their association with outcomes.* Diabetes Metab Syndr, 2021. **15**(1): p. 169-175.
62. Morrison, A.R., et al., *Clinical characteristics and predictors of survival in adults with coronavirus disease 2019 receiving tocilizumab.* J Autoimmun, 2020. **114**: p. 102512.
63. Nachtigall, I., et al., *Clinical course and factors associated with outcomes among 1904 patients hospitalized with COVID-19 in Germany: an observational study.* Clin Microbiol Infect, 2020. **26**(12): p. 1663-1669.
64. Ñamendys-Silva, S.A., et al., *Outcomes of patients with COVID-19 in the intensive care unit in Mexico: A multicenter observational study.* Heart Lung, 2021. **50**(1): p. 28-32.
65. Ren, L., et al., *Corona Virus Disease 2019 patients with different disease severity or age range: A single-center study of clinical features and prognosis.* Medicine (Baltimore), 2020. **99**(49): p. e22899.
66. Sun, Y., et al., *Independent and combined effects of hypertension and diabetes on clinical outcomes in patients with COVID-19: A retrospective cohort study of Huoshen Mountain Hospital and Guanggu Fangcang Shelter Hospital.* J Clin Hypertens (Greenwich), 2021. **23**(2): p. 218-231.
67. Tu, Y., et al., *Risk factors for mortality of critically ill patients with COVID-19 receiving invasive ventilation.* Int J Med Sci, 2021. **18**(5): p. 1198-1206.
68. Wang, F., et al., *Epidemiological characteristics of patients with severe COVID-19 infection in Wuhan, China: evidence from a retrospective observational study.* Int J Epidemiol, 2021. **49**(6): p. 1940-1950.
69. Xiong, S., et al., *Clinical characteristics of 116 hospitalized patients with COVID-19 in Wuhan, China: a single-centered, retrospective, observational study.* BMC Infectious Diseases, 2020. **20**(1): p. 787.
70. Yan, Y., et al., *Clinical characteristics and outcomes of patients with severe covid-19 with diabetes.* BMJ Open Diabetes Research & Care, 2020. **8**(1): p. e001343.
71. Zhang, N., et al., *Risk Factors for Poor Outcomes of Diabetes Patients With COVID-19: A Single-Center, Retrospective Study in Early Outbreak in China.* Front Endocrinol (Lausanne), 2020. **11**: p. 571037.