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Prevalence and outcome of newly diagnosed diabetes in COVID-19 patients: A systematic review

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REVIEW

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ABSTRACT

Background
Patients with COVID-19 with diabetes mellitus (DM) are reportedly more likely to develop severe clinical course and increased mortality.

Aims
We aimed to investigate the prevalence of newly diagnosed DM in COVID-19 patients and observe the association of underlying DM with increasing incidence of serious adverse events and mortality in COVID-19 patients.

Methods
We searched PubMed/Medline, Cochrane, Google Scholar, and Embase/Ovid for relevant articles that match our inclusion criteria. We assessed the quality of studies using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Our outcomes of interest were mainly the prevalence of ICU admissions and mortality.

Results
The pooled proportion of newly diagnosed DM in hospitalized COVID-19 patients was 44.5 per cent. We report that newly diagnosed diabetics indicate a poor prognosis of COVID-19 compared with non-diabetics or previously-known DM. We also show that COVID-19 patients with newly diagnosed DM are at increased risk of getting ICU admissions compared with patients with pre-existing DM.

Conclusion
We show that 44.5 per cent of hospitalized COVID-19 patients are likely to develop DM. We also confirm that DM worsens the prognosis of COVID-19 patients and raises the incidence rates of both ICU admissions and mortality.

Key Words
Diabetes, COVID-19, prevalence

What this review adds:

1. What is known about this subject?
It is well-established that the presence of comorbidities such as diabetes mellitus (DM) and hypertension (HTN) among patients contribute to increasing their risk of experiencing disease-related complications.

2. What new information is offered in this review?
We show that 44.5 per cent of hospitalized COVID-19 patients are likely to develop DM. We also confirm that DM worsens the raises the incidence rates of both ICU admissions and mortality.

3. What are the implications for research, policy, or practice?
DM should be adequately controlled in COVID-19 patients.

Introduction

The coronavirus 2019 (COVID-19) pandemic is still posing a public health threat worldwide because of its high transmission rate.[1] Mainly, people with COVID-19 present with mild to moderate symptoms of fever, dry cough, and tiredness. However, most symptoms do not require intensive care unit (ICU) admissions.[2] Although in some patients, this infection may lead to severe complications like pneumonia and respiratory failure.

With the consecutive rise in the threat of the COVID-19 crisis, an international effort is ongoing to explore the severity of the disease and the complications it is creating on health conditions.[3,4] The elderly population with concomitant comorbidities like hypertension (HT), type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD) are much likely to develop severe symptoms of COVID-19, which may require hospitalization and intensive care unit (ICU) admission.[5]

The evidence in the literature has shown that patients with COVID-19 who also have some comorbidities like DM are more likely to develop severe clinical course and increased mortality.[6,7] Recent reports show an increase in the incidence of newly diagnosed DM in COVID-19 patients. Furthermore, the incidence of acute new-onset DM among COVID-19 patients is considerably higher than patients with other causes of pneumonia.[8] The data available in the literature regarding newly detected DM in patients with COVID-19 contain a small sample size, and heterogeneity among them is inevitable.[9] Additionally, most of the data presented about the prevalence of DM in patients with COVID-19 are somewhat unclear and need further research and investigation.[10]

Therefore, the present systematic review investigates the prevalence of newly diagnosed DM in COVID-19 patients and observes the association of underlying DM with severity and mortality in COVID-19 patients.

Methods

This systematic review was designed by following methods described in the Cochrane Handbook for Systematic Reviews of Interventions,[11] as well as guidelines presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12]

Search strategy

Detailed search strategies for each electronic database were developed. The search key terms were based on the one used for PubMed/Medline, Cochrane, Google Scholar, and Embase/Ovid but with appropriate database-related modification of the search strategy, such as using truncations, wildcards, and filters. These key search terms included “corona virus”, “COVID-19”, “SARS-CoV-2”, “severe acute respiratory syndrome”, “diabetes”, “hyperglycaemia”, “new-onset diabetes”, “newly diagnosed diabetes”, “transient hyperglycaemia”, and “secondary hyperglycaemia”.

Searching other resources

We conducted a grey literature search in DOAJ to identify studies not indexed in the databases listed above. We also checked the references of all the included studies as well. Furthermore, we used the citation alert to look up more up-to-date publications and recent studies.

Search validation and data selection

Newly diagnosed DM was defined as new-onset DM (no prior history of DM with fasting plasma glucose (FPG) ≥7.0mmol/l or random blood glucose (RBG) ≥11.1mmol/l, and HbA1c <6.5 per cent). Previously undiagnosed DM was defined as (FPG ≥7.0mmol/l or RBG ≥11.1mmol/l, and HbA1c ≥6.5 per cent).[13]

Inclusion criteria for studies

- Design that included randomized controlled trials, nonrandomized controlled trials (Case-control or controlled cohort), observational studies and case series.
- Study population that included adult patients’ above18 years old.
- Confirmed diagnosis of DM or newly diagnosed DM with COVID-19.
- Studies reporting prevalence rates in addition to the outcome of ICU admission, mechanical ventilation, and in-hospital mortality.

Exclusion criteria for studies

- Review articles, opinion articles, case reports.
- Studies that did not define COVID-19 severity or did not include baseline physiologic data.
- Retracted studies.
- Studies that reported probable COVID-19 only.
- Duplicate patient data (from the same source and capture period) with preference given to sample size and quality for inclusion.
- Studies published in a language other than English.

Data Extraction and Analysis

The following data were extracted: study characteristics (author, geographic location, design, sample size, and start and end date), participant characteristics (age, sex, smoking status, total number of patients, number of patients with newly diagnosed DM, definition of newly diagnosed DM, comorbidities), presenting symptoms, admission pathologic data, and pulmonary radiologic findings (radiographic and CT imaging, organ system dysfunction, complications, the severity of illness scores, and outcome data (ICU admission, mechanical ventilation, hospital length of stay, and in-

hospital mortality rate).

The methodological quality of studies was evaluated through the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[14]

Results

Literature Search

Our electronic search of multiple databases yielded 819 preliminary studies; then, we removed duplicate studies, and 526 studies remained. The initial title and abstract screening further excluded 437 articles because they were case reports, case series, letters, commentaries, or review articles. Finally, 89 articles were filtered out for full-text screening. After reviewing the full text of these articles, a total of 78 studies were eliminated, of which twenty-four were overlapping cohorts, thirty-one studies were conducted only among patients without DM, and twenty-four did not satisfy the criteria of newly diagnosed DM. Finally, 11 studies[15-25] were selected for this systematic review for qualitative analysis. The PRISMA flow diagram (figure 1) demonstrates the process of screening these articles. While going through this phase of our systematic review, we carefully followed the guidelines of preferred reporting items for systematic review and meta-analysis (PRISMA).[12]

Characteristics of studies

A total number of 3478 patients were admitted in these eleven included studies from seven different countries, UAE, China, Italy, Singapore, Saudi Arabia, Mexico, and Austria. The majority of studies were from China,[16,21,22,25,26] two from Italy,[17,23] one from Singapore,[24] one from Austria,[19] one from Saudi Arabia,[18] one from UAE,[15] and one from Mexico.[20] The main characteristics of all these included studies with descriptions of their included patients are reported in (Table 1). These studies were retrospective and prospective in nature. Some of them were single-center, and some of them were multicenter studies. These studies were relatively new; almost all of them were published in the year 2020, and only one study, Vargas-Vazquez et al., was published this year, 2021. The risk of bias of individual studies was assessed based on the National Heart, Lung, and Blood Institute Study Quality Assessment Tools[27] (Table 2).

Prevalence of newly diagnosed DM in COVID-19 patients

All of our included studies reported the prevalence of DM in patients with COVID-19, and some of them mentioned the prevalence of DM in mortality cases. The newly diagnosed DM with COVID-19 patients was studied in eight studies, Bhatti et al.,[15] Li et al.,[16] Liu et al.,[25] Fadini et al.,[23] Tee et al.,[24] Sourij et al.,[19] Vargas-Vázquez et al.[20] and Zhang et al.[22] The prevalence of newly diagnosed DM in each study was reported differently. The prevalence of DM in a cohort study by Tee et al. was 7.9 per cent (19 of 240 patients); of these 19 patients, 14 (73.7 per cent) patients were newly diagnosed with DM.[24] Fadini et al. reported about 413 patients who tested positive for SARS-CoV-2 upon PCR analysis. Of these, 107 (25.6 per cent) were diabetics and graded as follows: 86 had pre-existing DM, and 21 had newly diagnosed DM patients.[23] Studies findings are presented in Table 3.

COVID-19 patients and complications of DM

The study by Li et al.[21] reported that COVID-19 patients with newly diagnosed DM who required admission to ICU were 11.7 per cent, and those who needed invasive mechanical ventilation (IMV) were 11.7 per cent. Known as T2DM, on the other hand, the ICU admission rate and IMV were 6.2 per cent and 4.7 per cent, respectively. They also discussed that newly diagnosed DM at the first measurement of hospital admission and a history of DM were associated with an increased risk of all-cause mortality in hospitalized COVID-19 patients.[16] Particularly, three studies reported an association between increased level of HbA1c levels and clinical severity of COVID-19.[10,16, 25]

The results of Fadini et al. analysis found that newly diagnosed DM patients had a higher primary composite outcome of ICU admission or death with a relative risk (RR) of 3.06; 95 per cent CI 2.04–4.57) and showed a stronger association with the invasive mechanical ventilation (IMV), admissions to ICU and mortality than pre-existing DM (with RR 1.55, 95 per cent CI 1.06–2.27).[23]

Comparing newly diagnosed diabetics with non-diabetic COVID-19 patients

Present studies show that newly diagnosed DM is associated with more adverse events, but these reports are not conclusive and require further assessment. Zhang et al.[22] reported that 27 per cent of the admitted patients in their study had DM; 42.9 per cent of them were newly diagnosed. Compared to patients with average fasting glucose, patients with impaired fasting glucose had higher mechanical ventilation at 3 per cent *vs.* 10 per cent and mortality rate at 2 per cent *vs.* 13 per cent, respectively. After adjusting for age, sex, and comorbidities, impaired fasting glucose increased the risk of mortality (Hazard Ratio (HR) =4.11; 1.15–14.74).[22]

In their study, Yumin et al. compared the outcomes in COVID-19 patients with DM, with and without hyperglycaemia (>11mmol/L) upon admission. Patients with hyperglycaemia were more likely to require intensive care unit care (21.4 per cent *vs.* 9.2 per cent), to develop acute respiratory distress syndrome (ARDS) (23.2 per cent *vs.* 9.2 per cent) and acute cardiac injury (12.5 per cent *vs.* 1.3 per cent), and had a higher death rate (19.6 per cent *vs.* 5.3 per cent).[16]

Comparing previously diagnosed diabetics with newly diagnosed diabetic COVID-19 patients

In Austria, a cohort study by Sourij et al. on hospitalized COVID-19 patients with established DM and pre-diabetes showed that in-hospital mortality reached 24.4 per cent.[19] Vargas-Vazquez et al. 2021 reported that newly diagnosed DM cases had higher odds of getting severe COVID-19 (with OR 9.13, 95 per cent CI 3.21–30.64), as compared with previously diagnosed DM (with OR 5.10, 95 per cent CI 1.98–15.91) and pre- diabetes (OR 3.85, 95 per cent CI 1.50–11.95).[20] Liu et al.[25] reported in their retrospective observational study that the prevalence of DM in patients with non-mild COVID-19 cases was 34.3 per cent.

Among patients with DM, 45.0 per cent were unaware of their underlying DM condition before admission and were newly diagnosed after hospitalization for COVID-19.[25] In fact, newly diagnosed DM was independently associated with an increased risk of in-hospital death in patients with COVID-19. In the study of Li et al., the mortality rate was 20 (21.3 per cent) in newly diagnosed DM and 11 (11.2 per cent) in known DM.[16]

Previous multiple studies have discussed the coagulation abnormalities common in severe COVID-19 patients with DM and were manifested by a higher level of d-dimer concentrations. In their study, Yumin Li et al. showed that a level of d-dimer more than 1.5lg/mL was associated with greater odds of mortality rate. Similar findings were reported in a previous study in 191 patients with COVID-19.[16]

Discussion

This present systematic review confirms that patients with COVID-19 infection and newly diagnosed diabetics are at increased risk of getting ICU admissions compared with patients with pre-existing DM. Furthermore, DM is likely to play a role in the increased risk of mortality during infection. The prevalence of newly diagnosed DM in patients with covid-19 was 44.5 per cent, based on collected data from all studies mentioning newly diagnosed DM.[15,16,19-25]

Possible pathophysiological mechanisms

The immense proportion of newly diagnosed DM in COVID-19 patients may suggest a bidirectional relationship between DM and COVID-19 infection. Pre-existing DM predisposition complicated by COVID-19 infection course, resulting in metabolic complications, might cause the unregulated glucose level, which is observed in most cases and might be explained by an adaptive metabolic response to critical illness and inflammation that involves neuroendocrine and immune pathways leading to transient insulin resistance and increased hepatic glucose production.[28] In their study Bhatti et al.[15] reported that patients requiring subsequent intensive care unit (ICU) admission had higher levels of fibrinogen, D-dimer, ferritin, and C-reactive protein (CRP).[29]

The association between glucose metabolism disruption and SARS-CoV-2 is attributable to specific mechanisms of COVID-19 infection. High pancreatic expression of ACE2 receptors, the entry point of SARS-CoV-2 virus, in addition to the adaptive responses to critical illness, might contribute to the onset or worsening of hyperglycaemia in patients with COVID-19.[30] Moreover, Acute hyperglycaemia shows up-regulation of the ACE2 gene, which facilitates entry of SARS-CoV-2 virus inside the cells. On the other hand, concomitant use of ACE inhibitors and some anti-diabetic medications causes up-regulation of ACE2 expression, making the cells susceptible to the inflammatory cytokines response to the SARS-CoV-2.[31] This finding is reflective of the impaired inflammatory cytokine response observed in COVID-19 patients with DM. Multiple other studies have also demonstrated enhanced inflammatory response in diabetic patients with severe COVID-19 infection compared to non-diabetic patients. Yan et al.[32] compared the clinical characteristics and outcomes in 48 severe COVID-19 patients with DM and 145 patients with severe COVID-19 with non-diabetics in a retrospective observational study in China. They found that white cell count, neutrophil count, CRP, IL-2R, IL-6, IL-8, d-dimer, lactate dehydrogenase (LDH), and N-terminal pro-B- type natriuretic peptide (NT-proBNP) were elevated in patients with DM.[33] Hence, patients with DM were more likely to receive mechanical ventilation (IMV), more likely to get transferred to ICU, with a higher mortality rate.[34]

Although newly diagnosed DM in COVID-19 patients could be due to the stress response associated with severe illness or treatment with glucocorticoids, the injury to pancreatic beta cells and other mechanisms which are affected by COVID-19 should also be considered.[35]

Another possible explanation is following. In newly developed DM, irrespective whether DM was caused by COVID-19 or detected during the course, physicians are unaware of the condition of DM specific to each patient. Contrarily, in patients with known presence of DM, physicians are already aware of the preexisting DM conditions, knowing or speculating how to treat and how to deal with in the specific patient. This difference (i.e., newly onset versus preexisting-known DM) may somewhat account for the present findings.

Management of diabetic COVID-19 patients

Regarding the management of patients with DM and COVID-19, practical guidelines and recommendations have been published by an international panel for diabetes management in patients with COVID-19 in and out of the hospital settings.[36] The IDF has also published other general guidelines for diabetic patients, mainly highlighted for developing countries worldwide.[37]

According to the American Diabetes Association (ADA) guidelines, basal insulin or a basal plus bolus correction insulin regimen is the preferred treatment for non-critically ill hospitalized patients. Hence insulin is the treatment of choice in hospitalized COVID-19 patients.[38]

General preventive measures should be followed by people with DM, including frequent hand hygiene and strict social distancing. Telemedicine should be encouraged when possible to avoid unnecessary routine clinical visits and prevent person-to-person transmission.[39]

Since adequate DM control is associated with improved cellular immunity, people with DM should intensify treatment and optimize glycaemic control.[40] Equally important, better control of hypertension and dyslipidaemia should also be encouraged to achieve healthier glycaemic control.[40]

Conclusion

In conclusion, this systematic review of eleven studies with 3478 patients shows a pooled proportion of 44.5 per cent for newly diagnosed DM in hospitalized COVID-19 patients. Current reports have reported that newly diagnosed DM may present a greater risk for poor prognosis of COVID-19 than no DM or known DM, thus should be considered a risk factor predictor for the COVID-19 severity. After all, the most efficient way to overcome the unfavourable consequences is to reduce exposure to corona sources.

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PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

The project did not involve patients participating in research either directly (e.g., interviews, questionnaires) or indirectly (e.g., people permitting access to data). Hence, this project does not require an ethics review or submission of a Research Ethics Application Form.

Figures and Tables

Figure 1: PRISM flow diagram

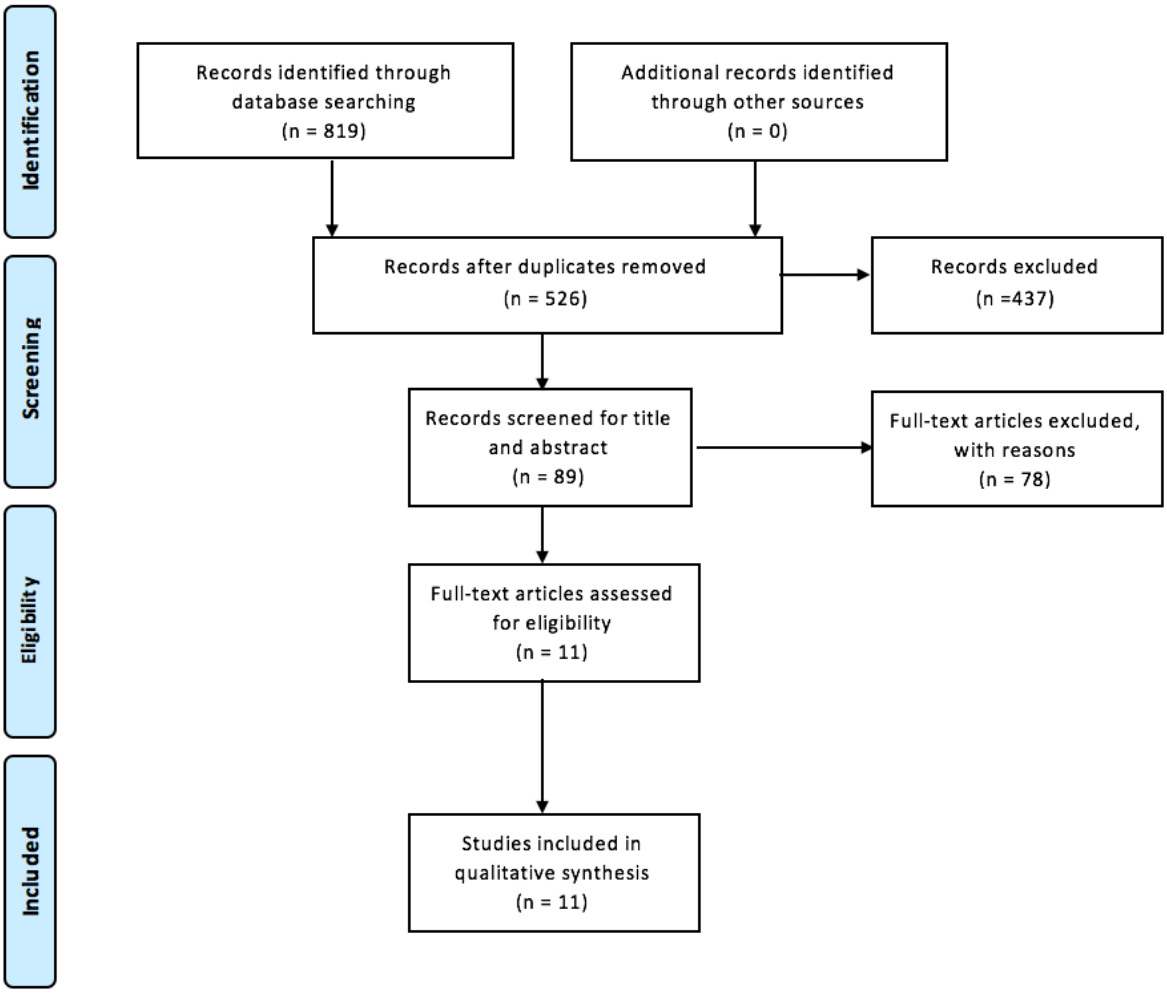

Table 1: Baseline characteristics of included studies

Study ID/Year	Location	Age (years); Mean(SD)	Study Type	Sample Size	Population	Study Quality
Bhatti et al. 2020[15]	UAE	54 (12.5)	Single-Center Cross-Sectional Study	513	COVID-19 patients, coexistent diabetes or pre-diabetes	Good
Li et al. 2020[16]	China	66.6 (11.5)	Retrospective observational study	453	COVID-19 patients with moderate disease, newly diagnosed diabetic patients	Good
Liu et al. 2020[25]	China	66.6 (12.2)	Retrospective study	373	COVID-19 patients, coexistent diabetes or pre-diabetes	Good
Fadini et al.2020[23]	Italy	64.9 (15.4)	A retrospective cohort study	413	COVID-19 patients, newly diagnosed diabetic patients	Good
Tee et al. 2020[24]	Singapore	44.2 (8.5)	Single-center retrospective study	240	COVID-19 hospital patients, newly diagnosed diabetic patients	Good
Sardu et al. 2020[17]	Italy	68.5 (5.8)	A retrospective study	187	COVID-19 patients	Good
Sheshah et al. 2020[18]	Saudi Arabia	60.45 (11.51)	Single-center, retrospective study	300	COVID-19 patients, coexistent diabetes	Good
Sourij et al. 2020[19]	Austria	71.1 (12.9)	Prospective and retrospective, multicenter, cohort study	238	COVID-19 patients, coexistent diabetes	Good
Vargas-Vázquez et al. 2021[20]	Mexico	52.0 (44.0–62.0)	Retrospective, observational study	317	COVID-19 patients, coexistent diabetes	Good
Yumin Li et al. 2020[21]	China	65 (57-71)	A retrospective cohort	132	COVID-19 patients, coexistent diabetes	Good
Zhang et al. 2020[22]	China	57 (38-66)	Multicenter retrospective cohort study	312	COVID-19 patients, newly diagnosed diabetic patients	Good

Table 2: Quality assessment of the included studies

Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Study Quality
Bhatti et al. 2020[15]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	NA	No	Good
Li et al. 2020[16]	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	Yes	No	NA	Yes	Good
Liu et al. 2020[25]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	NA	Yes	Good
Fadini et al.2020[23]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	Good
Tee et al. 2020[24]	Yes	Yes	CD	No	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	Good
Sardu et al. 2020[17]	Yes	Yes	CD	No	No	Yes	Yes	Yes	Yes	No	Yes	No	CD	Yes	Good
Sheshah et al. 2020[18]	Yes	Yes	CD	No	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	Good
Sourij et al. 2020[19]	Yes	Yes	CD	No	No	Yes	No	Yes	Yes	No	Yes	No	NA	Yes	Good
Vargas-Vázquez et al. 2021[20]	Yes	Yes	Yes	CD	No	Yes	Yes	No	Yes	No	Yes	No	NA	No	Good
Yumin Li et al. 2020[21]	Yes	Yes	Yes	CD	No	Yes	CD	No	Yes	No	Yes	No	CD	Yes	Good
Zhang et al. 2020[22]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	Good

Table 3: summary of the included studies' outcomes

Study ID	Newly Diagnosed Diabetes	Diabetes	HTN	COPD	CVD	HbA1c	Blood glucose Level (mmol/L)	CRP(mg/L)	Mechanical ventilation (MV)	ICU admissions	Mortality
Bhatti et al. 2020[15]	(15/103)14.6(%)	103/410)25(%)	66 (64.0(%))	1 (0.9(%))	11 (10.6)	7.7 (1.6)	Random:10.2(4.2)	64.1 (82.7)	NR	(29/103)28.2%	(5/103)4.9%
Li et al. 2020[16]	98	94	97	10 (10.6(%))	28	5.7-6.4	Fasting:8.86(0.21)	52.2 (4.00)	NR	Newly diagnosed diabetes:11 (11.7), Diabetes: 4 (4.1)	Newly diagnosed diabetes:20 (21.3),Diabetes: 11 (11.2)
Liu et al. 2020[25]	36 (45.0%)	44 (55.0%)	90 (38.6%)	20 (8.6%)	26 (11.1%)	6.4 (5.9–7.3)	Fasting:7.5(6.3–11.2)	NR	NR	NR	27 (11.6%)
Fadini et al.2020[23]	21/107	86/107	212 (51.3%)	29 (7.3%)	44 (11.0%)	6.1 (4.9–12.5)	Fasting:7.3±3.5	6.3 (2.5–12.3)	53 (12.8%)	NR	48 (11.6%)
Tee et al. 2020[24]	14 /19(5.8%)	19 of 240(7.9%)	18 (7.5%)	NR	NR	>7.0%	Random:7.8mmol/L	NR	NR	NR	NR
Sardu et al. 2020[17]	NR	8 (23.5)18 (72)	26 (76.5)18 (72)	NR	7 (20.6)5 (20)	NR	7.7mmol/L	NR	NR	NR	NR
Sheshah et al. 2020[18]	NR	5 (1.7)137 (45.7)	84 (28.0)	10 (3.3)	10 (3.3)	9.0 ± 2.5	Random:10.0±5.6	NR	21(7%)	NR	30 (10.0)
Sourij et al. 2020[19]	47 (19.8%)	180 (75.6)	169 (71.0)	48 (20.2)	63 (26.5)	6.4 (1.4)	6.97mmol	9.9 (14.8)	Diabetes:7 (14.9),Pre diabetes:50 (26.2)	Diabetes:8 (17.0),Pre diabetes:51 (26.7)	Diabetes:7 (14.9),Pre diabetes:51 (26.7)
Vargas-Vázquez et al. 2021[20]	125 (39,.4%%)	159 (50.2%)	31 (24.8)51 (46.8)	NR	2 (1.6)9 (8.3)	6.0(5.8–6.2)9.5(7.7–11)	6.27mmol/L11.22mmol/L	16.3 (9.1–25.0)16.3 (9.1–25.6)	5 (15.2)	5 (15.2)	2 (6.1)
Yumin Li et al. 2020[16]	NR	130(98.5%)	64.40%	6(4.5	13.60%	NR	9.35(7.1–13.8)	47.45(13.23–108.8)	10(7.6)	15(10–21)	21(16–28)

Zhang et al. 2020[22]	36(11.3%%)	84 (27%)	89 (29%)	12 (4%)	22 (7%)		Fasting:5.62 (5.07–6.88)	17.6 (3.8–41.3)	32 (10%)	9(3%)	33 (11%)