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Awadhesh Kumar Singh, Ritesh Gupta, Amerta Ghosh, Anoop Misra



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Diabetes in COVID-19: Prevalence, Pathophysiology, Prognosis and Practical Considerations

Awadhesh Kumar Singh^{1, @}, Ritesh Gupta², Amerta Ghosh², Anoop Misra^{2,3,4}

¹G.D Hospital and Diabetes Institute, Kolkata

²Fortis CDOC Hospital, Chirag Enclave, New Delhi

³National Diabetes, Obesity and Cholesterol Foundation, New Delhi

⁴Diabetes Foundation (India), New Delhi

[@] *Corresponding Author*

Highlights

1. High prevalence of diabetes is seen in patients with SARS-CoV-2 (COVID-19) and the presence of diabetes is a determinant of severity and mortality.
2. Diabetes might facilitate infection by COVID-19 due to increased viral entry into cell and impaired immune response.
3. Blood glucose control is important for all patients who have diabetes and COVID-19 infection.
4. Telemedicine can be very useful for the management of patients with diabetes in present times with limited access to healthcare facilities.

Abstract:

Background and Aims: High prevalence of diabetes makes it an important comorbidity in patients with COVID-19. We sought to review and analyze the data regarding the association between diabetes and COVID-19, pathophysiology of the disease in diabetes and management of patients with diabetes who develop COVID-19 infection.

Methods: PubMed database and Google Scholar were searched using the key terms ‘COVID-19’, ‘SARS-CoV-2’, ‘diabetes’, ‘antidiabetic therapy’ up to April 2, 2020. Full texts of the retrieved articles were accessed.

Results: There is evidence of increased incidence and severity of COVID-19 in patients with diabetes. COVID-19 could have effect on the pathophysiology of diabetes. Blood glucose control is important not only for patients who are infected with COVID-19, but also for those without the disease. Innovations like telemedicine are useful to treat patients with diabetes in today’s times.

Background:

The disease burden of coronavirus infectious disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) has been increasing continuously with more than a million confirmed patients and more than deaths globally [1]. With a high prevalence of diabetes, it is important to understand the special aspects of COVID-19 infection in people with diabetes. This becomes even more important, as most parts of the world are seeing restrictions on mobility of patients in order to contain the pandemic. Recently our group has published an article highlighting special considerations in the management of diabetes in today's times with COVID-19 pandemic [2]. Much more data from various parts of world has accumulated since then about the association between diabetes and COVID-19, management of diabetes in those with COVID-19 infection, and innovative strategies for medical consultation in view of limited access to healthcare facilities for patients with chronic diseases.

Aims of the Review:

This review aims to collate currently available data about diabetes and COVID-19 infection. It specifically looks at the relation between diabetes and COVID-19 in terms of epidemiology, pathophysiology and therapeutics. The review is updated

till the time of writing; however, the data is evolving, and the conclusions made here might change later.

Methods:

We searched PubMed database and Google Scholar using the key terms 'COVID-19', 'SARS-CoV-2', 'diabetes', 'antidiabetic therapy' up to April 2, 2020. Full texts of the retrieved articles were accessed.

Association of Diabetes with Acute Viral Pandemics in the Past:

Diabetes and associated complications can increase the risk of morbidity and mortality during acute infections due to suppressed innate and humoral immune functions. The levels of glycated hemoglobin (HbA1c) >9% have been linked to a 60% increased risk of hospitalization and pneumonia-related severity during bacterial infection [3]. Past viral pandemics have witnessed the association of diabetes to increased morbidity and mortality. Diabetes was considered as independent risk factor for complications and death during 2002-2003 outbreak of Severe Acute Respiratory Syndrome (SARS-CoV-1) [4]. Similarly, the presence of diabetes tripled the risk of hospitalization and quadrupled the risk of intensive care unit (ICU) admission during Influenza A (H1N1) infection outbreak in 2009 [5]. During the 2012 outbreak of Middle East Respiratory Syndrome Coronavirus (MERS-CoV), diabetes was prevalent in nearly 50% of population and the odds

ratio (OR) for severe or critical MERS-CoV ranged from 7.2 to 15.7 in diabetic cohort [6] as compared to overall population. Mortality rate in patients with MERS who had diabetes was 35% [7, 8].

Association of Diabetes in COVID-19 Patients:

Emerging data suggests that COVID-19 is common in patients with diabetes, hypertension, and cardiovascular disease (CVD), although the prevalence rate varied in different studies as well in country-wise data. In the pooled data from the 10 Chinese studies (n=2209) on characteristics of comorbidities in patients with COVID-19, Singh *et al* [9] have reported a prevalence of hypertension, diabetes and CVD in 21%, 11%, and 7% patients, respectively. Similarly, in a meta-analysis of 8 trials that included 46,248 COVID-19 patients, Yang *et al* [10] reported a prevalence of 17%, 8%, and 5% for hypertension, diabetes and CVD respectively, in patients with COVID-19. Similarly, Epidemiology Working Group of Chinese Center for Disease Control and Prevention that investigated 20, 982 patients of COVID-19 have shown that hypertension, diabetes and CVD were associated in nearly 13%, 5% and 4% of patients respectively [11]. In contrast, an Italian study by Onder *et al* found diabetes in nearly 36%, while CVD was associated in nearly 43% of 355 patients admitted with COVID-19 [12]. Similarly, in a small study of 24 patients from United States, Bhatraju *et al* [13] reported diabetes to be associated with 58.0% patient with COVID-19. While the study from the COVID-

19 surveillance group of Italy (n=481) has shown that 34% patients with COVID-19 had diabetes, the COVID-19 response team from Centers for Disease Control and Prevention (CDC), USA reported a prevalence of 11% from the data of 7,162 COVID-19 patients [14, 15]. Table 1 summarizes the prevalence of these comorbidities in all available studies to-date in patients with COVID-19 [11-27].

It should be noted here that these findings could be a mere reflection of the high prevalence of diabetes across the globe including China (being the diabetes capital of the world), and thus causality cannot be inferred from the observed elevated proportions.

Morbidity and Mortality in Diabetic Cohorts with COVID-19:

Evolving data also suggest that patients of COVID-19 with diabetes are more often associated with severe or critical disease varying from 14-32% in different studies [15-18, 20, 22, 24]. Wang *et al* [20] in a study of 138 patients reported that 72% patients of COVID-19 with comorbidities including diabetes required admission in ICU, compared to 37% of patients without comorbidities. In an analysis of 201 patients with COVID-19, Wu *et al* [24] found that diabetic patients had a hazard ratio (HR) of 2.34 (95% CI, 1.35 to 4.05; p=0.002) for acute respiratory syndrome (ARDS). However, in the meta-analysis of 8 studies (n=46,248) by Yang *et al* [10]

the odds ratio (OR) of severe COVID-19 was not significantly higher in patients with diabetes (OR, 2.07; 95% CI, 0.89 to 4.82), unlike hypertension (OR, 2.36; 95% CI, 1.46 to 3.83) and CVD (OR, 3.42; 95% CI, 1.88 to 6.22). Another meta-analysis of 9 studies from China (n=1936) by Chen *et al* [28] found a significant correlation between COVID-19 severity and diabetes (OR, 2.67, 95% CI; 1.91 to 3.74; $p<0.01$). Table 2 summarizes the prevalence of non-severe (mild to moderate) to severe or critical disease in patients with diabetes with COVID-19. Figure 1 illustrates the graphical representation of non-severe and severe COVID-19 in patients with diabetes.

Interestingly, the prevalence of non-survivors was also higher in diabetic subjects with COVID-19 and it varied from 22 to 31% in different studies [17, 21, 23, 24, 27]. Table 3 summarizes the prevalence of survivors and non-survivors among patients with diabetes and COVID-19. Figure 2 depicts the graphical representation of these data. In a univariate analysis of 191 patients with COVID-19, Zhou *et al* [21] found diabetes to have an OR of 2.85 (95% CI, 1.35 to 6.05; $p<0.001$) for in-hospital mortality. However, this association of diabetes and mortality was no longer significant after a multivariate regression analysis. Nevertheless, in a bivariate cox regression analysis, Wu *et al* [24] demonstrated a HR of 1.58 (95% CI, 0.80 to 3.13, $p=0.19$) for death in patients with diabetes with COVID-19.

In a summary report of 44,672 patients of COVID-19, The Chinese Center for Disease Control and Prevention reported a case fatality rate (CFR) of 2.3% (1023 deaths among 44,672 confirmed cases). However, the CFR was as high as 10.5% in patients with CVD, 7.3% in diabetes and 6.0% in hypertension [29]. Based on these findings and acknowledging the higher morbidities and mortality associated with comorbidities, researchers have recently proposed that the course of treatment and prognosis of COVID-19 should be stratified based on the absence or presence of co-morbidities into type A, B and C. While Type A represents COVID-19 patients with pneumonia with no comorbidities, Type B denotes COVID-19 pneumonia with comorbidities; and Type C denotes COVID-19 pneumonia with multi-organ dysfunction [30].

Special Aspects of Pathophysiology of Diabetes and Relationship of Anti-diabetic Drugs in the Context of COVID-19:

SARS CoV-2, like SARS CoV utilises ACE-2 as receptor for entry into cell [31]. ACE2 is expressed not only in the type I and II alveolar epithelial cells in the lungs and upper respiratory tract, but also several other locations like heart, endothelium, renal tubular epithelium, intestinal epithelium, and pancreas. S-glycoprotein on the surface of SARS CoV2 binds to ACE-2 and causes a conformational change in the

S-glycoprotein. This allows proteolytic digestion by host cell proteases (TMPRSS2 and Furin) ultimately leading to internalization of the virion [32]. Cellular entry of the virus triggers inflammatory response with recruitment of T helper cells which produce interferon γ . This leads to recruitment of other inflammatory cells leading to a 'cytokine storm' which could lead to organ damage and multi-organ failure seen in severe disease.

As discussed, diabetes is associated with poorer outcomes in COVID-19. A study in 161 patients with COVID-19 in Wuhan found increased time for viral clearance in patients with diabetes [33]. Apart from the usual mechanisms (impaired neutrophil chemotaxis and phagocytosis) by which diabetes predisposes to infections in general, there are several specific factors responsible for increased risk and severity of infection with SARS CoV2 in diabetes

a) *Increased ACE-2 Expression*: Diabetic mice have been found to have increased expression of ACE-2 in renal cortex, liver and pancreas, but not in lungs [34]. Recently, a genome-wide Mendelian randomization study found diabetes to be causally related to ACE-2 expression [35]. Though the significance of these observations is not clear at present, increased ACE-2 expression might predispose people with diabetes to infection with SARS CoV2.

- b) Increased Furin:* Diabetes is associated with an increase in furin, which is a type-1 membrane-bound protease, belonging to the proprotein convertase subtilisin/kexin family (PCSK). It is involved in the entry of coronaviruses into the cell and increased Furin has been reported in diabetes, which might facilitate viral replication [36].
- c) Impaired T-Cell function:* Alterations in CD4 lymphocytes have been reported in animal models with MERS [37]. Lymphocytopenia has been observed in patients with COVID-19 and correlated with prognosis [17].
- d) Increased Interleukin-6 (IL-6):* Several cytokines are increased in COVID-19 infection. Amongst these, IL-6 is increased in diabetes and may play a more deleterious role in Covid-19 infection [38]. Monoclonal antibody against IL-6 receptor (tocilizumab) is being tested in a trial in COVID-19 [39].

Effect of SARS CoV2 on Blood Glucose

ACE-2 receptors are expressed in pancreatic islets and infection with SARS CoV has been seen to cause hyperglycaemia in people without pre-existing diabetes. Hyperglycaemia was seen to persist for 3 years after recovery from SARS indicating a transient damage to beta cells [40]. Though the similar

effect has not been reported in COVID-19, it may be important to monitor blood glucose levels in acute stage and during follow up.

Role of Antidiabetic Drugs in Current Context

There is no data on the differential effects of oral antidiabetic drugs on the disease course in COVID-19. Metformin has antiproliferative and immunomodulatory effects by virtue of inhibition of AMP activated protein kinase and has shown protective role in pneumonia in mouse models [41]. In one study in patients with tuberculosis, patients treated with metformin had better survival than those who did not receive metformin [42]. In a median 6.2 years of follow up of 5266 patients with diabetes, Mendy *et al* [43] showed that metformin was significantly associated with a decreased risk of mortality in patients with chronic lower respiratory diseases (HR: 0.30, 95% CI, 0.10 to 0.93), even after the adjustment for multiple confounding factors. In a study of 4321 patients with a follow up of 2-year period, Ho *et al* [44] showed metformin users had a significantly lower risk of death (HR, 0.46; 95% CI, 0.23 to 0.92), compared with non-metformin users, in patients with coexistent chronic obstructive pulmonary disease and diabetes. Thiazolidinediones (TZD) seen to increase the risk of pneumonia in a study when compared to sulfonylureas [45]. Experimental studies suggest that pioglitazone reduces steatohepatitis by increasing the ACE2 expression in liver tissues [46]. This purported increase in ACE2 expression and its relation to COVID-19 has led

some researchers to propose avoiding TZD in patients with diabetes and COVID-19. Experimental studies also suggest that liraglutide, a GLP-1 receptor agonist increases the ACE2 expression in lungs in type1 diabetic rat and improves right ventricular hypertrophy [47]. Implications of these findings in the current context of COVID-19 and its relation to anti-diabetic drugs is not yet fully clear.

Role of DPP4 Enzyme and DPP4 Inhibitors

Dipeptidyl peptidase-4 (DPP4) are tissue oligopeptides involved in multiple biological processes that include control of the activity of growth factors, chemokines and bioactive peptides and T-cell activation beside regulating glucose metabolism [48]. The relationship of coronavirus to this cellular type-II transmembrane protein DPP4 (CD26) has generated a great interest recently. DPP4 serves as the receptor for MERS-CoV, in the same way as ACE-2 is the receptor for SARS CoV and SARS CoV2. [49, 50]. Experimental studies have suggested that certain polymorphisms of DPP-4 are associated with reduced chance of MERS-CoV infection [51]. This finding might explain the perplexing absence of MERS-CoV cases in Africa, despite the presence of virus in camels, presumably because of frequent presence of protective polymorphisms of DPP-4 in Africans [51]. Moreover, this has generated an immense interest whether use of DPP4 inhibitors (DPP4i) can reduce the viral entry of MERS-CoV. In one *in vitro* study,

sitagliptin, vildagliptin and saxagliptin could not block the coronavirus viral entry into cells [52].

Though ACE-2 is recognized as the main receptor for SARS CoV-2, a recent modeling study did not rule out its interaction with CD26 or DPP4 [53]. Moreover, a possible interaction of DPP4 and renin-angiotensin system (RAS) pathways seems to be plausible, although not completely studied. Interestingly, dipeptidyl aminopeptidase I-III cleaves the Angiotensin II (1-8) to Angiotensin III (2-8) and IV (3-8) which has cascading favorable effect through Angiotensin-4 (AT-4) receptors. Similarly, various endo- and oligo-peptidase cleaves Angiotensin I (1-10) directly to Angiotensin (1-7) which has a very favorable cascading effect. This suggest that a plausible interaction of non-specific DPP-4i with ACE2 is theoretically possible, and therefore, this area needs a future research.

In this regard, some of the studies found that co-administration of angiotensin-converting enzyme inhibitors (ACE-I) with DPP4 inhibitors led to an increased sympathetic tone and a consequent adverse hemodynamic effect [54-56]. There has been an interaction observed between ACE-I and vildagliptin where a 4- to 5-folds increased risk of angioedema was noted possibly due to the diminished degradation of bradykinin or substance P [57]. In contrast, in the experimental study, sitagliptin

was shown to inhibit ACE which could partially explain the purported beneficial CV effects [58].

DPP4 inhibitors have been associated with an increased risk of upper respiratory infections, however these agents have not been shown to lead to increased risk of pneumonia [45]. At present, there is insufficient evidence either for or against the use of DPP-4i in patients with diabetes and COVID-19 [59].

Special Aspects of Management of Diabetes with COVID-19:

Glycemic control

Glycemic control is important in any patient who has COVID-19. Though there is limited data about the association of blood glucose levels with disease course in COVID-19 at present, data from other infections like SARS and influenza H1N1 has shown that patients with poor glycemic control have increased risk of complications and death [60, 61]. Most patients with mild infection and with normal oral intake can continue the usual antihyperglycemic medications. However, it is advisable to discontinue SGLT-2 inhibitors because of the risk of dehydration and euglycemic ketosis. Metformin may also need to be stopped if there is vomiting or poor oral intake. Doses of other antihyperglycemic drugs like sulfonylureas and insulin may have to be altered depending upon the blood glucose levels.

Most hospitalized patient with COVID-19, especially those with respiratory distress, would require insulin. Ideally, patients with very poor oral intake or those on mechanical ventilation would require intravenous insulin infusion with frequent monitoring of blood glucose (every hour or every two hours, see next section). However, the adjustment of infusion rates would necessitate visit to the patient and increase exposure to the medical personnel. There is a need to explore alternate insulin administration strategies. One of these is use of subcutaneous short acting insulin analogues, an approach which has been used successfully in mild to moderate diabetic ketoacidosis; however, its safety in critically ill patients is less clear [62, 63]. Secondly, single dose of basal insulin has been attempted in critically ill patients as in one study from Thailand. This could be an attractive option as it would reduce contact with the patient considerably [64] but needs more research especially in critically sick patients. Finally, insulin pump or continuous subcutaneous insulin infusion (CSII) could be an option and some models have the advantage of altering the insulin rates remotely via Bluetooth [65]. Fully automated closed-loop glucose control has been tried in critical illness and if feasible, could be useful in treating patients with COVID-19 [66].

Blood glucose monitoring

Blood glucose monitoring poses a special challenge as it necessitates frequent visits to patient's bedside, especially if the patient is critically ill and receiving

intravenous insulin. However, attempts could be made to minimize exposure. If the patient is not critically ill, he/she may be given a glucose testing device and self-monitoring may be taught. Blood glucose readings can then be communicated on phone and necessary action taken. Continuous glucose monitoring (CGM) could be of help, especially the systems where the data can be remotely accessed without visiting the patient. Though, there is some evidence of CGM interference with commonly prescribed medications like acetaminophen, atenolol and lisinopril, it has been shown to be useful and reliable in critically ill patients [67, 68].

Role of ACE/ARBs

Treatment with ACE inhibitors and ARB has the potential to cause up regulation of ACE2[67]. Mice with coronavirus induced lung injury showed improvement when treated with an angiotensin receptor blocker, losartan [70]. A retrospective analysis showed reduced rates of death and endotracheal intubation in patients with viral pneumonia who were continued on ACE inhibitors [71]. However, a contrary view is that increased expression of ACE2 could theoretically increase the risk of infection with SARS CoV-2. This could be a concern in people with diabetes who are at already elevated risk of infections because of many other factors. However, there is no evidence to support this hypothesis currently. In a retrospective analysis of 112 COVID-19 hospitalised patients with cardiovascular disease in Wuhan, there was no significant difference in the proportion of ACEI/ARB medication

between non-survivors and survivors [72]. In view of lack of robust evidence for either benefit or harm, it is reasonable for patients to continue using ACE inhibitors and ARB, as recommended by European Society of Cardiology Council on Hypertension, European Society of Hypertension and American Heart Association [73-75].

Role of Statins, Calcium Channel Blockers and Aspirin

There are several studies about the protective effect of statins in pneumonia [76]. Statins are known to increase ACE-2 levels and may protect against viral entry of SARS CoV2 [77]. Also, statins are known to inhibit Nuclear factor kappa B (NF κ B) activation and might help in blunting the cytokine storm [78].

Calcium channel blockers (CCB) have been shown to reduce severity of disease and mortality in patients with pneumonia, presumably by inhibiting calcium influx into the cell [79]. The precise role of these agents in COVID-19 has not been studied, however it seems safe to continue these drugs for control of blood pressure in hypertensive patients. Since CCB has no effect on ACE2 expression, some researchers have proposed its preferable use in patients with COVID-19 and hypertension [80].

Though aspirin has anti-inflammatory properties, it may not be advisable to continue it in patients with sepsis and disseminated intravascular coagulation.

However, in patients with underlying coronary artery disease, it needs to be continued as anticoagulant unless otherwise contraindicated.

Treatment of Diabetes in Times of COVID-19 Pandemic:

Treatment of diabetes poses challenge in the current times when the world is going through an unprecedented pandemic. There are ‘lockdowns’ in most places with people confined at home. Opportunities for exercise are limited and regular walks and visits to gyms or swimming pools are not possible. There is also considerable mental stress because of the unpredictability of the disease as well as social immobility. Alterations in the daily routine affect the dietary intake as well. Stress could lead to inappropriate eating. Access to fresh fruits and vegetables could be limited and there may be a tendency to eat packaged foods high in calories, saturated fat and *trans*-fat. Patients may find it difficult to procure medicines, insulin, needles and glucose strips etc. because of partial or complete lockdowns. The problem becomes more pronounced with elderly who are living alone. All these factors could cause glucose dysregulation and could predispose the patients to complications like infections, hyperosmolar coma, ketoacidosis and even acute cardiac events.

Measures for good health in patients with diabetes

1. Patients with diabetes need to maintain regularity in daily diet. Care should be taken not to vary the calorie intake markedly. Healthy balanced diet with good amount of protein, fiber and limitation of saturated fats is important to maintain a good glycemic control.
2. Exercise should be continued. Home based exercise like cycling, treadmill, stationary jogging and resistance exercise with small weights are beneficial.
3. Regular intake of antidiabetic drugs and insulin is important and should be emphasized.
4. Telemedicine can be very helpful in these times. Patients can consult their physician via telemedicine and appropriate advice about treatment can be given [81]. An article dealing with telemedicine is under publication in the special issue.
5. Care of feet should be emphasized in order to avoid foot related complications. There are telemedicine temperature mats which can screen for inflammation without having to visit the clinic. The patients who show inflammation can then be called to the clinic [82].
6. Patients need to be educated about the need to visit the hospital urgently in emergency situations like vomiting, drowsiness, shortness of breath, chest pain, weakness of limbs, altered sensorium etc.

Conclusion:

Diabetes is associated with increased incidence and severity of COVID-19. There is experimental evidence of the effect of diabetes on viral entry into cell and inflammatory response to the infection. It is important to control blood glucose in patients who are infected with COVID-19. Treating diabetes at present with restrictions on movement is challenging; however, innovations like telemedicine can be useful in these trying times.

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Journal Pre-proof

Table 1: Prevalence of diabetes, hypertension and other co-morbidities in COVID-19:

First author	n	Smokers, %	HTN, %	Diabetes, %	CVD, %	COPD, %	CKD, %	CLD, %	Ref.
COVID-19 in China									
Liu <i>et al</i>	61	6.6	19.7	8.2	1.6	8.2	NR	NR	16
Guan <i>et al</i>	1099	12.6	15.0	7.4	3.8	1.1	0.7	NR	17
Huang <i>et al</i>	41	7.3	14.6	19.5	15.0	2.4	NR	2.4	18
Chen <i>et al</i>	99	NR	NR	12.1	40.0	1.0	NR	NR	19
Wang <i>et al</i>	138	NR	31.2	10.1	19.6	2.9	2.9	2.9	20
Zhou <i>et al</i>	191	6.0	30	19.0	8.0 [#]	3.0	1.0	NR	21
Zhang <i>et al</i>	140	NR	30	12.1	8.6	1.4	1.4	NR	22
Yang <i>et al</i>	52	4.0	NR	17.0	23.0	8.0	NR	NR	23
Wu <i>et al</i>	201	NR	19.4	10.9	4.0	2.5	1.0	3.5	24
Guo <i>et al</i>	187	9.6	32.6	15.0	11.2 [#]	2.1	3.2	NR	25
Liu <i>et al</i>	137	NR	9.5	10.2	7.3	1.5	NR	NR	26
Chen <i>et al</i>	274	7.0%	34.0	17.0	8.0	7.0	1.0	NR	27
CCDCP, China	20,982	NR	12.8	5.3	4.2	2.4	NR	NR	11
COVID-19 in Italy									
Onder <i>et al</i>	355	NR	NR	35.5	42.5	NR	NR	NR	12
Covid-19 surveillance group, Italy	481	NR	73.8	33.9	30.1 [#]	13.7	20.2	3.7	14
COVID-19 in USA									
Bhatraju <i>et al</i>	24	22	NR	58.0	NR	4.0	21.0	NR	13
CDC COVID-19 Response Team, USA	7162	3.6	NR	10.9	9.0	9.2	3.0	0.6	15
# reported coronary heart disease only, HTN- hypertension, CVD- cardiovascular disease, COPD- chronic obstructive pulmonary disease, CKD- chronic kidney disease, CLD- chronic liver disease, NR- not reported, Ref.- references, CCDCP- Chinese Center for Disease Control and Prevention, CDC- Centers for Disease Control and Prevention									

Table 2: Prevalence of non-severe versus severe COVID-19 in patients with diabetes:

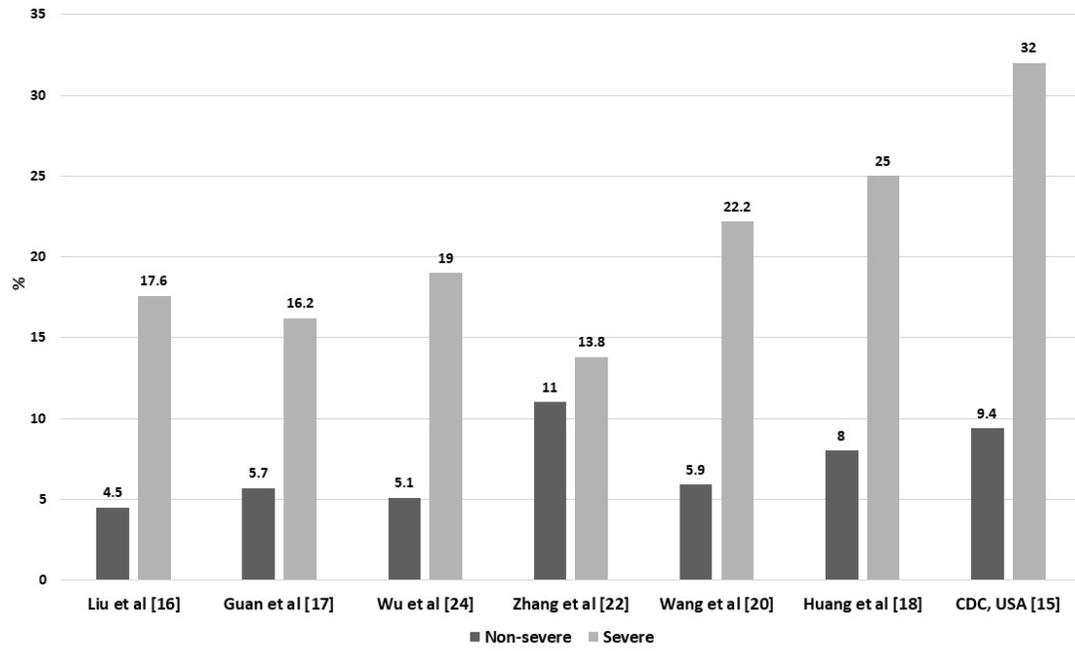
Study	n	DM (n, %)	Non-severe/Non- ICU care [Mild/ moderate] (%)	ICU care [Severe/Critical] (%)	p value between non-severe vs. severe COVID-19	Ref.
Liu <i>et al</i>	61	5 (8.2%)	4.5%	17.6%	0.094	16
Guan <i>et al</i>	1099	81 (7.4%)	5.7%	16.2%	NR	17
Wang <i>et al</i>	138	14 (10.1%)	5.9%	22.2%	0.009	20
Wu <i>et al</i>	201	22 (10.9%)	5.1%	19.0%	0.002	24
Zhang <i>et al</i>	140	17 (12.1%)	11.0%	13.8%	0.615	22
Huang <i>et al</i>	41	8 (15%)	8.0%	25.0%	0.16	18
CDC COVID-19 Response Team, USA	7162	784 (10.9%)	9.4%	32.0%	NR	15

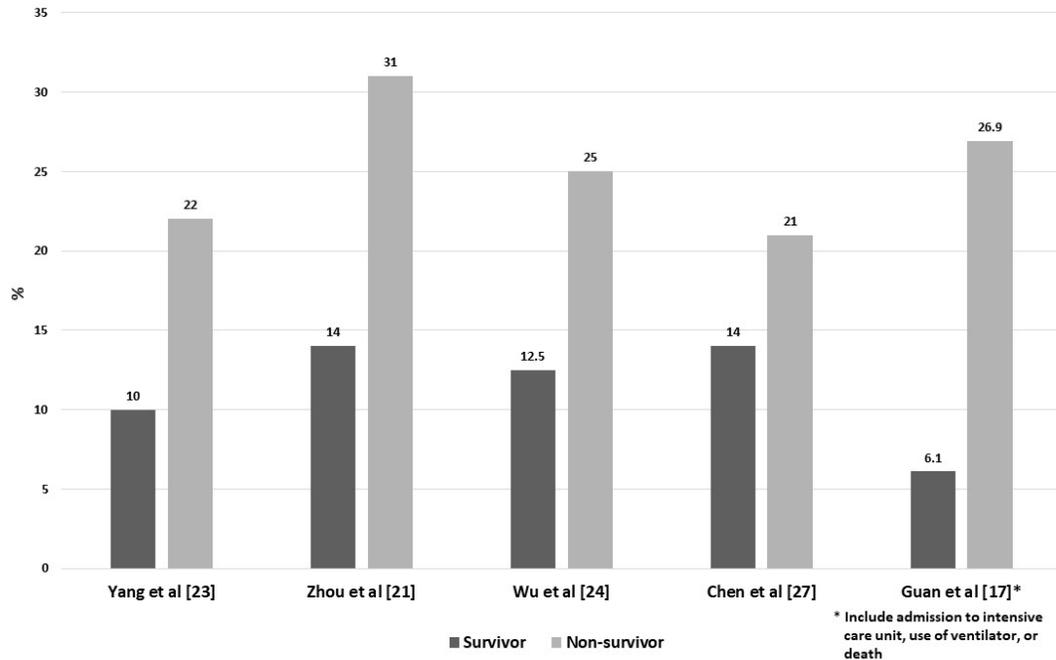
DM- diabetes mellitus, NR- not reported, ICU- intensive care unit, Ref. References, CDC- Centers for Disease Control and Prevention

Table 3: Prevalence of survivor versus non-survivor in COVID-19 patients with diabetes:

Study	n	DM (n, %)	Survivor of COVID-19 (%)	Non-survivor of COVID-19 (%)	p value Between non-severe vs. severe	Mortality rate	Ref.
Yang <i>et al</i>	52	9 (17%)	10%	22%	NR	NR	23
Zhou <i>et al</i>	191	36 (19.0%)	14.0%	31.0%	0.0051	OR 2.85; 95% CI, 1.35 to 6.05; p<0.001	21
Wu <i>et al</i>	88	16 [#] (18.2%)	12.5%	25.0%	NR	HR 1.58; 95% CI, 0.80 to 3.13, p=0.19	24
Chen <i>et al</i>	274	47 (17.0%)	14.0%	21.0%	NR	NR	27
Guan <i>et al</i>	1099	81 (7.4%) [@]	6.1% [@]	26.9% [@]	NR	NR	17

with ARDS – acute respiratory distress syndrome; [@] Primary composite end point includes admission to intensive care unit, use of mechanical ventilator, or death, OR- odds ratio, HR- hazard ratio, NR- not reported, DM- diabetes mellitus, Ref.- references





Conflict of interest

We hereby declare that we have no conflict of interest related to this article.

Awadhesh Kumar Singh

Ritesh Gupta

Amerta Ghosh

Anoop Misra

Journal Pre-proof