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

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International Diabetes Federation

Review

Diabetes and COVID-19: A systematic review on the current evidences

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ABSTRACT

Background: COVID-19 pneumonia is a newly recognized illness that is spreading rapidly around the world and causes many disability and deaths. Some diseases, for instance diabetes, is continuously suggested as a risk factor which contributes to the severity and mortality of COVID-19. However, to date, there are no comprehensive studies aiming to explain the exact relationship between diabetes and COVID-19. Thus, this study aims to summarize the evidence about diabetes and COVID-19 outbreak through a systematic review and meta-analysis approach.

Method: A literature review was implemented within databases of Scopus, PubMed, Science direct, and Web of science. Observational reviews, case-report, and case-series studies that assessed the diabetes in COVID-19 patients, were included. Data extraction and assessment were guided by PRISMA checklist.

Findings: Some studies suggest that there were no significant differences in symptoms between patients who suffered from both diabetes and COVID-19 and those who only suffered COVID-19. In the subsequent meta-analysis 14.5% of the subjects were diabetic patient. These clients have poor ARDS prognosis, severe symptoms, and the death rate is higher among COVID-19 patients. In addition, it is suggested the diabetic patients will be treated with antibiotics, antivirals, and HCQ.

Conclusion: The results of this study show that diabetes is a risk factor – and contributes to the severity and mortality of patients with COVID-19. This paper also provides recommendations and guidelines for which could be useful for prevention and treatment of diabetic patients affected by COVID-19.

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Contents

1. Background

Diabetes mellitus (DM) is a disease and an international health threat, the severity of which has increased in the last twenty years [1]. In 1985, 30 million people suffered from diabetes, and by 2010 that figure increased to 285 million. According to the latest global estimate from the International Diabetes Federation that number of affected patients in 2019 stands at 463 million. It is estimated that by 2045, around 700 million people will suffer from diabetes [2,3]. Diabetes is the leading cause of end-stage renal disease, adult-onset blindness, and non-traumatic lower extremity amputations [4]. Diabetic complications cause more disability, and at the extreme, life-threatening disorders [5].

In early December 2019, the first pneumonia cases of an unknown origin were identified in China. The pathogen has been identified as a novel enveloped RNA beta-coronavirus [6]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia quickly became a newly recognized illness that was spreading rapidly throughout Wuhan (Hubei province) to other provinces in China, and continues to spread around the world [7]. The World Health Organization (WHO) pronounced the official name of SARS-CoV-2-induced disease as the coronavirus disease 2019 (COVID-19). By April 28th 2020 (8 pm), the number of patients has risen sharply – 2,959,929 people are infected with this virus and the official death toll stands at 202,733 [8,9]. Fever, dry cough, dyspnea, fatigue, and lymphopenia are identified as the symptoms of patients with COVID-19 [10]. Clinical manifestations are very similar to those of severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS) [7,11,12]. It is mainly transmitted by droplets or direct contact, feces and infected through the respiratory tract [13,14]. Due to novelty of disease, the factors affecting the severity of status and death remain unknown. Nevertheless, it is assumed that patients with underlying health conditions, people of older age, and delayed referral to a hospital all contribute to the severity of the symptoms [15–17]. Patients with underlying health conditions such as high blood pressure and diabetes are considered as the high-risk group for catching the novel corona virus. Furthermore, it is considered that such patients are likely to suffer further complications and the risk of death from COVID-19 is higher in this group [15]. COVID-19 also has indirect effects on people with underlying health conditions. For instance, as COVID-19 continues overwhelm many health care systems across the globe, large number of non-COVID-19 patients are left without the necessary health care service they need due to their previous conditions. Furthermore, many have been affected by the reduced physical activities caused by the lockdowns introduced by most governments across the globe – which is of specific importance

for those who suffer from diabetes. All of these implications should be considered problematic as they increase the risk of infections, hospitalization, amputations, and possibly death in diabetes patients [18].

The increased rate of those suffering from diabetes combined with the prevalence of COVID-19 suggests that the care for diabetic patients must be increased in order to reduce any further complications and the risk of death. Due to a lack of studies on the relationship between COVID-19 and diabetes, it is difficult to suggests how exactly that increased care should look like. Thus, in this paper, we aim to fill the lacunae in the existing literature, and conduct a study that reviews current evidence and provides guidelines for prevention and treatment of people affected by both COVID-19 and diabetes.

2. Methods

2.1. Protocol and registration

A protocol for this review was registered in Kermanshah University of medical sciences. The focus of the review was narrowed to diabetes patient's status in COVID-19 pandemic and related factors.

2.2. Eligibility criteria

Inclusion of publications that were observational studies, such as cohort, case-report and case-control research. Additionally, we included letters, viewpoints, and review studies that provide further advice about diabetes. The editorials or review studies that just summarize other studies were excluded. Studies considered focused on those that reported diabetes in COVID-19 patients.

2.3. Search strategy

An unrestricted search to 31 March 2020 in Scopus, PubMed, Science direct, and Web of science was executed. We developed search strategies using keywords and Mesh terms of diabetes, Corona, COVID, and SARS-CoV2. In addition, reference lists of eligible articles were screened for further relevant studies and systematic reviews scanned for appropriate references.

2.4. Search validation and data selection

All pertinent articles were discovered by using the search terms and those that were available on the indicated databases during the period of this review were included. All articles not meeting the inclusion criteria as stated above were later discarded. Citations were downloaded into Endnote X8. Two authors (PAS and MJ) independently reviewed all titles and abstracts for irrelevant studies. Potentially eligible manuscripts were exported. At this stage, the selected papers were screened again to identify articles relevant to diabetes and COVID-19 and eliminated those duplicated. We obtained the full text of the remaining articles and examined them independently. Results were compared and any controversies surrounding any particular included or excluded paper were resolved by discussion. Data extraction was performed independently using a standard extraction form. The studies were subsequently screened for reporting diabetes and COVID-19.

2.5. Data extraction and report

Data extraction was performed in a Garrard table [19]. The studies were subsequently screened for reporting factors that could influence diabetes and COVID-19. The characteristics of each study and the method are described and presented in the table, in which, patients, the prevalence of diabetes in COVID-19 patients, and also related factors are reported. Furthermore, mortality rate and advices for patients or treatment are raised by the Garrard table. For studies that reported more than one data, we included all of them. We performed the Meta-analysis for prevalence of diabetes in COVID-19 patients using comprehensive meta-analysis (CMA) software. Because of high heterogeneity ($I2 = 93.66$ $P < 0.001$), we used random effect analysis to combine the studies. Publication bias was calculated using Egger test, and funnel plot. The descriptions of the extracted data are guided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [20].

3. Result

3.1. Study selection

We find 197 studies in initial search. After removing duplicates, 177 references remained. By initial evaluation on the title and abstract, 65 citations were selected for full-text review. Of these, 50 were considered eligible for final appraisal. Eighteen studies were excluded due to the lack of data on the diabetes-suffering among the COVID-19 patients. Eventually, we included 27 manuscripts in this review. We adhered to reporting and guidance based on the preferred reporting items for systematic review and meta-analysis (PRISMA) statement (Fig. 1).

3.2. Characteristics of studies

These 27 studies were published between December 2019 and 31 March 2020. Fourteen studies were retrospective. Majority of the studies were conducted in China. These studies applied in all types of diabetes. But in three studies, patients with type2 diabetes are considered [21,22,17]. Because a number of studies include similar samples, it is impossible to estimate the actual number of patients assessed. However, 76,639 patients were reported, with study sample sizes varying between 1 [17] and 72,314 [23] patients, overall (for further details see: Table 1).

3.3. Purpose of the studies

The main purpose of the study was not a comprehensive study of people who suffer from diabetes and are infected with COVID-19 (please see Table 1). There are seven separate studies about diabetes and how to treat diabetic patients dur-

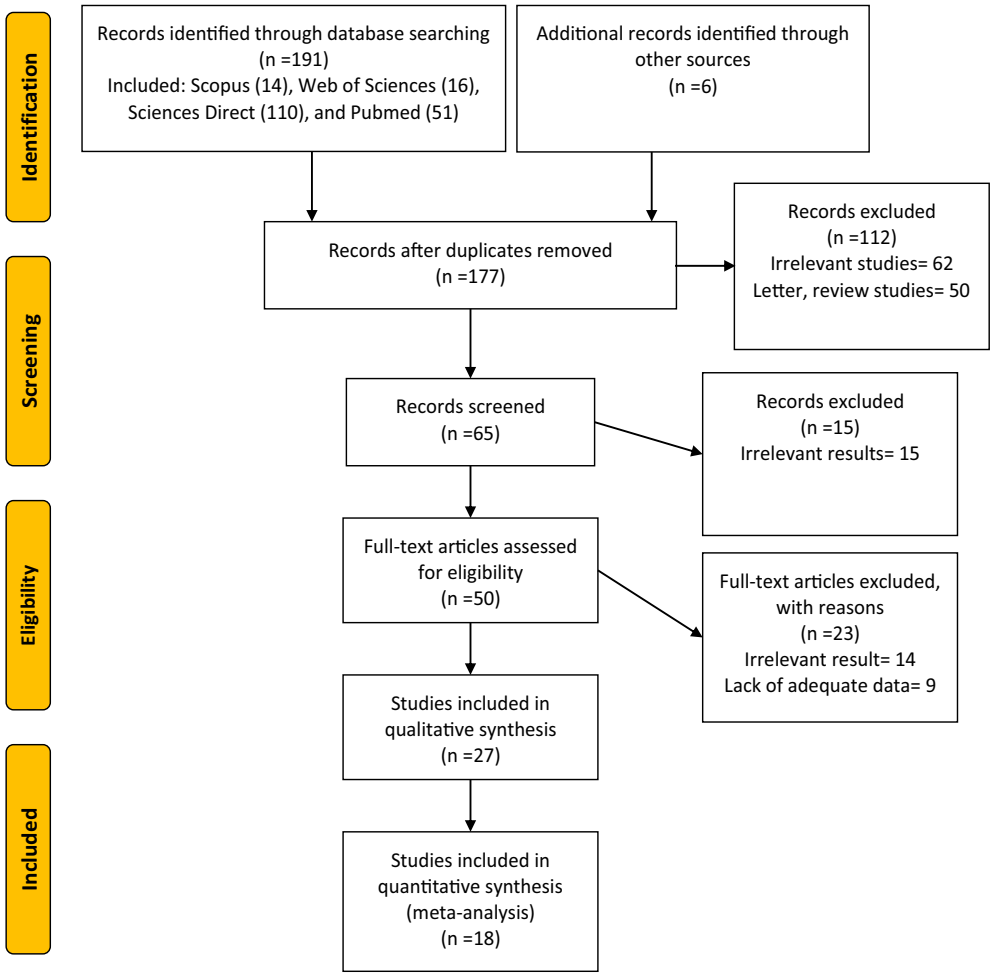

Fig. 1 – PRISMA flow diagram for the literature search and study selection.

ing the pandemic of COVID-19. There has been, to date, a single study examining one diabetic patient who also suffered from COVID-19 using a case-study method.

3.4. *Prevalence of diabetes in COVID-19 patients*

Eighteen studies report prevalence of diabetes in patients with COVID-19 and one study report prevalence of diabetes in mortality cases. Because of heterogeneity between patients and study design, and also, lack of data from several countries, further studies must be conducted for more complete information of diabetes in patients with COVID-19. In six studies, the prevalence of diabetes was ≤10% that it was 128 diabetes patients in 2333 patients with COVID-19 included Wang (15/242) [24], Guan (81/1099) [16], Wan (12/135) [25], Hui (2/41) [22], Yang (9/710) [26], and Chen (9/106) [27]. Fourteen studies report prevalence in 10.1–20% that it was 216 diabetes patients in 1559 patients with COVID-19 included Shi (10/81) [28], Zhao (4/37) [29], Hu (47/323) [30], Zhang (17/140) [10], Zhou (36/191) [31], Wang (54/339) [32], Wang (14/138) [33], Wu (22/201) [34], and Liu (12/109) [35]. And three studies report prevalence above 20% that it was 171 diabetes patients in 404 patients with COVID-19 included Xu (147/355) [36], Bhatraju (14/24) [37], and Li (10/25 death) [38]. The results of meta-analysis on 18 studies has 14.5% of the subjects with diabetes (Fig. 2), in which there was no publication bias (t = 1.06 P = 0.304). (Fig. 3)

3.5. *Symptoms of patients with both diabetes and COVID-19*

Only one study reported symptoms of the patient with both diabetes and COVID-19 [17]. This study was a case-report study, in which the patient had Fever (38.6 °C), cough, congested pharynx, mild swelling of the bilateral tonsils, coarse breath without rales, decrease of blood oxygen saturation, increased percentage of neutrophils and lymphocytes, decreased total protein and albumin, elevated serum glycated hemoglobin, and elevated ESR and CRP. It seems that these symptoms, except blood glucose and glycated hemoglobin, may be have neither differences with other patients, so recommended for further studies [39].

3.6. *Care and treatment of patients and advice to patients and health-care systems*

Because of the novelty of the COVID-19 disease, there is no data which could provide insights into the possible special

Table 1 – Characteristics of included Studies (n = 27).

Author, Title, Journal	Year	Purpose	Study design [a]
Shi et all. [28] Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study; *The Lancet Infectious Diseases*	2020	Describe the CT findings across different timepoins throughout the disease course	Retro
Zhao et all. [29] Anesthetic Management of Patients with COVID 19 Infections during Emergency Procedures; *Cardiothoracic and Vascular Anesthesia*	2020	prevent cross-infection in the operating room during emergency procedures for patients with 2019-nCoV by following anesthesia management protocols	Retro
Onder et all. [44] Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy; *JAMA*	2020	Case-Fatality Rate and Characteristics of Patients in Italy	Viewpoint
Xu et all. [36] Acute kidney injury at early stage as a negative prognostic indicator of patients with COVID-19: a hospital-based retrospective analysis; *medRxiv*	2020	Study described acute kidney injury (AKI) at early stage of COVID-19 and its clinical significance.	Retro
Wang et all. [24] Epidemiological and Clinical Features of Corona Virus Disease 2019 (COVID-19) in Changsha, China; *The Lancet Infectious Diseases*	2020	provide a basis for exploring effective prevention, and control of COVID-19.	Case-series
Hu et all. [30] Risk Factors Associated with Clinical Outcomes in 323 COVID-19 Patients in Wuhan, China; *medRxiv*	2020	Identify risk factors associated with clinical outcomes for improving management guidelines	Retro
Guan et all. [16] Clinical Characteristics of Coronavirus Disease 2019 in China; *New England journal of medicine*	2020	Analysis of cases throughout mainland China might help identify the defining clinical characteristics and severity of the disease.	Retro
Wu et all. [23] Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention; *JAMA*	2020	Epidemiologic Characteristics of the COVID-19 patients	Viewpoint
Yang et all. [26] Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study; *Lancet Respiratory Medicine*	2020	Describe the clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia	Retro

Table 1 – (*continued*)

Zhou et all. [21] Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China; *Metabolism Clinical and Experimental*	2020	Assessment of blood glucose management in diabetic patients	Retro
Zhang et all. [10] Clinical characteristics of 140 patients infected with SARSCoV- 2 in Wuhan, China; *Allergy*	2020	Investigate the clinical characteristic and allergy status of patients infected with SARS-CoV-2	Retro
Zhou et all. [31] Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study; *The Lancet*	2020	Risk factors for mortality and a detailed clinical course of illness, including viral shedding in COVID-19 patients	Retro
Wang et all. [32] Coronavirus Disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up *Journal of Infection*	2020	To investigate the characteristics and prognostic factors in the elderly patients with COVID-19	Retro
Wang et all. [40] Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed; *Diabetes Research and Clinical Practice*	2020	Blood glucose management for the outbreak of 2019 novel coronavirus disease	Review
Wang et all. [33] Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China; *JAMA*	2020	To describe the epidemiological and clinical characteristics of novel coronavirus (2019-nCoV)–infected pneumonia	Retro
Wu et all. [34] Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China; *JAMA*	2020	Describe the clinical characteristics and outcomes in patients with COVID-19 pneumonia who developed acute respiratory distress syndrome (ARDS) or died	Retro
Wan et all. [25] Clinical Features and Treatment of COVID-19 Patients in Northeast Chongqing; *Medical Virology*	2020	Provide the international community with a deeper understanding of COVID-19	Case-series

Table 1 – (*continued*)

Bhatraju et all. [37] Covid-19 in Critically Ill Patients in the Seattle Region — Case Series *New England journal of medicine*	202	Describe the demographic characteristics, coexisting conditions, imaging findings, and outcomes among critically ill patients with Covid-19	Case-series
Rogers et all. [18] All Feet On Deck—The Role of Podiatry During the COVID-19 Pandemic: Preventing hospitalizations in an overburdened healthcare system, reducing amputation and death in people with diabetes; *American Podiatric Medical Association* communication	2020	Reduce the burden on the healthcare system by keeping diabetic foot and wound patients safe, functional, and at home.	Special
Li et all. [38] Clinical characteristics of 25 death cases with COVID-19: a retrospective review of medical records in a single medical center, Wuhan, China; *medRxiv*	2020	Summarize the clinical characteristics of death cases with COVID-19 and to identify critically ill patients of COVID-19 early and reduce their mortality	Retro
Hui et all. [22] Clinical and radiographic features of cardiac injury in patients with 2019 novel coronavirus pneumonia; *medRxiv*	2020	Investigate the correlation between clinical characteristics and cardiac injury of COVID-2019 pneumonia.	Retro
Chen et all. [27] Hypertension and Diabetes Delay the Viral Clearance in COVID-19 Patients; *medRxiv*	2020	Detect the underlying diseases that could impact on viral clearance.	Pros
Han et all. [17] A Diabetic Patient with 2019-nCoV (COVID-19) Infection Who Recovered and Was Discharged from Hospital; *Thoracic imaging*	2020	Report a patient with both diabetes and COVID-19	Case-report
Iacobucci et all. [41] Covid-19: diabetes clinicians set up social media account to help alleviate patients' fears; *BMJ*	2020	set up a social media account to help alleviate patients' fears around covid-19 and provide them with "a secure base" of information.	Pros
Singh et all. [42] Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries; *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*	2020	Review existing literature and relevant websites regarding Chloroquine and hydroxychloroquine and COVID-19, adverse effects related to drugs, and related guidelines.	Review

Table 1 – (continued)

Gupta et all. [43]	2020	Suggestion measures for diabetes patients to prevention of COVID-19	Review
Clinical considerations for patients with diabetes in times of COVID-19 epidemic; *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*			
Liu et all. [35]	2020	Describe the clinical features of 109 hospitalized COVID-19 patients and further discuss the clinical characteristics, treatment, and progression of patients who developed into ARDS.	Pros
Clinical Characteristics and Progression of 2019 Novel Coronavirus Infected Patients Concurrent Acute Respiratory Distress Syndrome; *medRxiv*			

[a] Retro, Retrospective; Pros, Prospective.

treatments that could be useful for diabetes patients with COVID-19. Only one study reported treatment of one patient with both diabetes and COVID-19 and further study may be change this results [17]. Six studies made suggestions for diabetes patients [21,40,18,41–43]. Most of these suggests are based on past results and expert opinions. In the case-report research, patient may be being treated with antibiotics (meropenem, linezolid), antiviral agents (ganciclovir, oseltamivir), and symptomatic treatment with unknown medications [17]. There were four studies which resulted in specific recommendations advocated by health-care systems on how to treat patients who suffer from diabetes. The recommendations focused on diabetic patients, some of whom are not infected with COVID-19, and in patients with COVID-19. The COVID-19-diabetic patients should be managed for blood glucose and glycemic control; in-home visits, self-monitoring, higher acuity office visits, telemedicine; use of social media, and remote patient monitoring. The doctors instructed an immediate decrease in all unnecessary diabetes-related hospital admissions, as well as shield the patients from hospital-based care. It is further advised that additional attention must be given to nutrition and adequate protein intake, daily exercise, and taking influenza and pneumonia vaccines for these people [41,18,21,43]. The suggestions for patients with both diabetes and COVID-19 included glucose control, declining the adverse effects of drugs, avoid anti-hyperglycemic agents, reduce dosage of anti-diabetic medications, and stopping oral agents, especially metformin and sodium glucose cotransporter-2 inhibitors for critically ill patients. These patients should be isolated for 14 days or until resolving the symptoms. They may need adequate hydration, symptomatic treatment with acetaminophen, steam inhalation, measurement of blood glucose and urinary ketones in type-one of diabetes if fever with hyperglycemia occurs, and using of Insulin instead of oral anti-glycemic agents [40,43]. In one study, hydroxychloroquine (HCQ) is proposed, because it is approved for treatment of diabetes in India. In addition, there is a need for further research on diabetes and COVID-19, a subgroup where significant mortality has been shown [42] (Table 2).

These results are based on current findings that have bias in examined population, so they may become more complete in future studies by finding other results.

3.7. *Complications of diabetes in COVID-19 patients*

Current research suggested that diabetes has an impact on clinical outcomes, but these reports are not conclusive and require further examination. Hu reports that diabetes is a predicting factor for unfavorable clinical outcomes [30]. In Shi study, one patient who died of COVID-19 was 73 years old and had type2 diabetes [28]. Xu, report that comorbidity with diabetes is important independent risk factors predicting AKI among COVID-19 patients [36]. In Onder's study, 126 patients from 355 died patients had diabetes (35.5%) versus, only three patients (0.8%) of patients that died had no disease [44]. Wang's study on 242 patients, showed the higher prevalence of diabetes among severe patients (4/37, 10.8) than non-severe patients (11/205, 5.4%) [24]. Hu study reported higher prevalence of diabetes outcomes included severe (22/146,

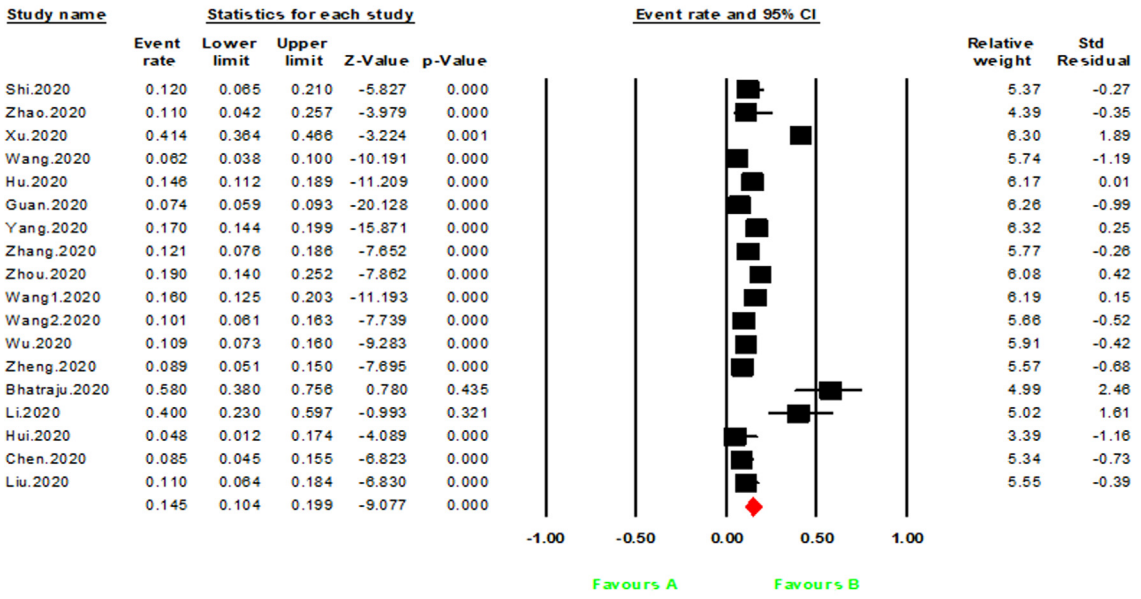

Fig. 2 – The prevalence of diabetic patients among COVID-19 patients.

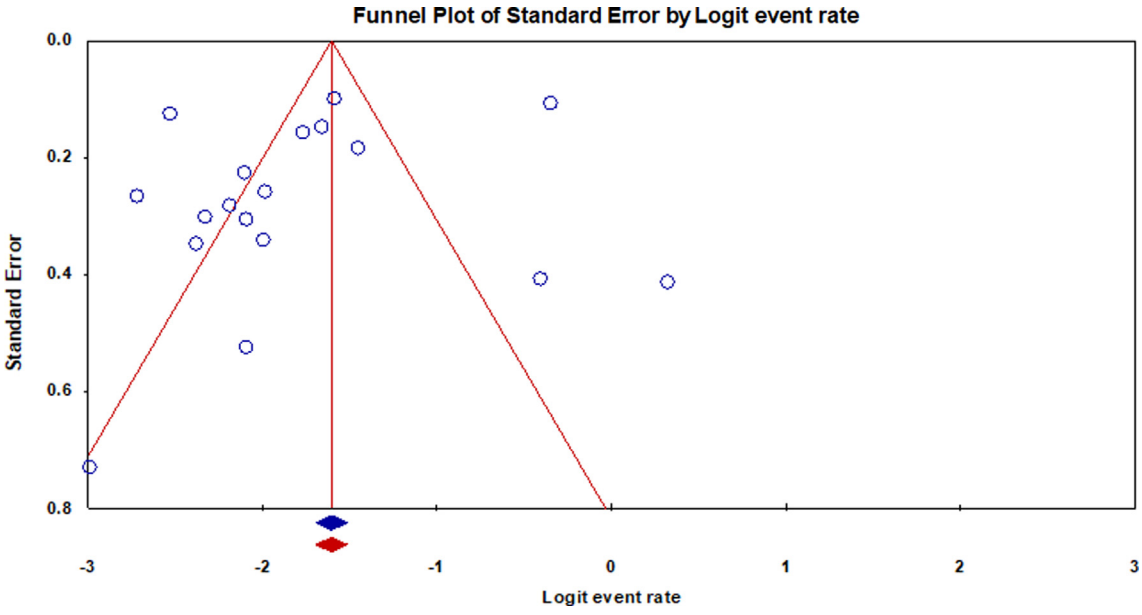

Fig. 3 – Funnel plot of the studies.

15.1%) versus non-severe (14/151, 9.3%), Critical (11/26, 42.3%), and Favorable (28/260, 10.8%) against unfavorable (19/63, 30.2%) [30]. Similarly, in Guan study the prevalence of diabetes was higher in the severe patients than non-severe (28/173, 16.2%, VS. 53/926, 5.7%) [16]. In Wu, the mortality rate of COVID-19 among diabetic patients was 7.3%, higher than overall mortality rate (2.3%) [23]. In another study, among 52 critically ill patients, the prevalence of diabetes was (2/20, 10%) in survivors and (7/32, 22%) in non-surviving patients [26]. In 140 patients (severe, 58; non-severe, 82) the prevalence of diabetes was (8, 13.8%) and (9, 11%), respectively [10]. Similarly, in 191 patients include severe (137) and non-severe (54), the prevalence of diabetes was 19 (14%) and 17 (31%), respectively [31]. Also, in Wang's study on 339 patients (274 severe and 65 Non-severe); the prevalence of diabetes was higher in severe patients (43, 15.8%) than non-severe (11, 17.2%)

Table 2 – Care and treatment of patients and advice to patients and health-care systems.

Study	Treatment/Suggestion
Zhou et all. [21]	1. Management of blood glucose
Wang et all. [40]	1. Blood glucose should be controlled for all patients during hospitalization 2. Reduction adverse drug reaction 3. During the 4-week follow-up period after discharge, blood glucose homeostasis should be maintained continuously and patients need to avoid infectious diseases due to a lower immune response 4. Long-term follow-up
Rogers et all. [18]	1. In-home visits 2. Higher acuity office visits 3. Telemedicine 4. Remote patient monitoring 5. Avoid unnecessary diabetes-related hospital admissions 6. Shift Away from Hospital-Based Care
Han et all. [17]	1. Symptomatic treatment 2. Antibiotics (meropenem, linezolid) 3. Antiviral agents (ganciclovir, oseltamivir)
Iacobucci et all. [41]	1. Social media account
Singh et all. [42]	1. Use of hydroxychloroquine (HCQ)
Gupta et all. [43]	**Specific Measures in Patients with Diabetes:** 1. Good glycaemic control and self-monitoring blood glucose 2. Attention to nutrition and adequate protein intake 3. Exercise 4. Take influenza and pneumonia vaccinationsGeneral Preventive Measures 1. Handwashing with soap and water 2. Use of alcohol-based hand rubs 3. There is a need to practice proper respiratory hygiene with covering of mouth and nose with bent elbow or tissue when coughing or sneezing. Touching of mouth, nose and eyes should be avoided. 4. Contact with an affected person needs to be minimized. Use of recommended face masks is advised if there is a contact with someone with respiratory symptoms. 5. Avoid the travel to major affected areasMeasures in Patients of diabetes with COVID 19 infection 1. Affected person needs to be isolated for 14 days or till the symptoms resolve 2. Hydration should be maintained and symptomatic treatment with acetaminophen, steam inhalation etc. can be given 3. Patients with type 1 diabetes should measure blood glucose and urinary ketones frequently if fever with hyperglycemia occurs 4. Anti-hyperglycemic agents that can cause volume depletion or hypoglycemia should be avoided. Dosage of oral anti-diabetic drugs may need to be reduced. Patients should follow sick day guidelines and may need more frequent monitoring of blood glucose and drug adjustment 5. Hospitalised patients with severe disease need frequent blood glucose monitoring. Oral agents especially metformin and sodium glucose cotransporter-2 inhibitors need to be stopped 6. Insulin is the preferred agent for control of hyperglycemia in hospitalized sick patients

[32]. In a study on 135 patients (mild 95 and 40 severe), the prevalence of diabetes was higher in severe (9, 22.5%) than mild patients (3, 3.1%) [25]. In another study on 138 patients include 36 ICU patients and 102 non-ICU; the diabetes was (8, 22.2%) in ICU patients and (6, 5.9%) in non-ICU [33]. In the other study, Wu showed Diabetes and glucose level have significant correlation with ARDS ($P = 0.002$, $P < 0.001$). The prevalence of diabetes was higher in ARDS patients (with ARDS 16/84, 19%; non-ARDS 6/117, 5.1%) and died patients with ARDS (died 11/44, 25%; alive 5/40, 12.5%) [34]. Similarly, Liu's study reported that diabetes had a significant relation with ARDS ($P = 0.002$). Prevalence of diabetes in this study was higher in ARDS patients than non-ARDS (11/53, 20.8%; 1/56, 1.8% respectively) [35]. Chen reported that diabetes may cause prolonged clearance of COVID-19 from patients [27].

4. Discussion

Diabetes is one of the most common diseases, and the leading cause of multiple expensive complications; if it occurs in young patients, it can exclude them from the workforce. Additionally, COVID-19 disease is a novel respiratory illness that spreads across the world and to date it infected above 2.9 million people and resulted in around 202,000 deaths. We identified 27 studies about diabetes and COVID-19 in systematic search. The aim of most studies was not diabetes, directly. The majority of the studies were conducted in China. Due to the differences between in diabetes in the populations [45,46], it is important to conduct more studies on other populations. The cumulative prevalence of diabetes in COVID-19 patients was 14.5%. As for diseases similar to COVID-19, the overall prevalence of diabetes was 54.4% in MERS, and for H1N1 influenza it was 14.6% [47]. It should be noted that some studies overlapped patients with each other. Overall symptoms of COVID-19 in all patients are sore throat, fever, dry cough, fatigue, and diarrhea [48,31]. In diabetic patients, there is no certain data about different symptoms, and they are more likely with other patients [17]. In international diabetes federation (IDF) statement reported that symptoms in diabetes patients not different with other COVID-19 patients [49]. But there is an agreement that symptoms are more developed among diabetic patients [25,24].

Various studies reported that patients with diabetes are more likely than healthy people to develop COVID-19 disease and complications such as ARDS and even death. Hu reported that diabetes was a predicting factor for unfavorable outcomes and prevalence of diabetes was higher in severe patients than non-severe patients in studies on 1451 patients [50,16,30,25,24,32,10,31]. Also, other nine studies, clearly indicate that diabetes is the risk factor for poor outcomes and related with ARDS and prolonged cure in COVID-19 patients [30,35,44,28,33,34,23,36,26]. In an irrelevant study on 113 patients with septic shock, a history of diabetes was associated with a lower risk of developing ARDS compared with non-diabetics [51]. This result needs further investigation. For other similar diseases, such as SARS and MERS, an identical finding has been reported. A study conducted on 144 patients with SARS showed that presence of diabetes was associated with a poor outcome [52]. In another study, conducted on 8422 patients with SARS, one of the risk factors for death was diabetes [50]. Similarly in other studies, the presence of diabetes mellitus was linked with adverse outcomes [53,54]. The same results are also presented about MERS patients, in which diabetes is one of the risk factors for poor outcome, and the primary comorbidity connected with severe or lethal MERS infection [55–59].

It is well documented that diabetes increases the severity of the COVID-19 disease. However, the pathology is not clear. Understanding the interaction between diabetes and COVID-19 could open a window for therapeutic measures, but there is a paucity of data on this issue. The results of a study on MERS and diabetes concluded virus replication, and clearances are not influenced by diabetes [58]. Conversely, Chen concluded diabetes would prolong the clearance of COVID-19 [27]. This controversy may be due to the differences between viruses or samples. The other advocated reason is blocking the activity of Dipeptidyl Peptidase IV (DPP4) enzyme that is caused by antidiabetic drugs. These drugs, known as gliptin, target the activity of DPP4, thus increasing insulin secretion and decreasing blood-glucose levels. DPP4 is an aminopeptidase in the cell membrane that plays a role in various physiological processes, including the immune responses [58,60,61]. Reducing the macrophage function has been supported by some researchers as the other cause of higher severity of COVID-19 among diabetic patients [62]. In Iacobellis's study, chronic hyperglycemia and inflammation are introduced as the possible reason of an abnormal and ineffective immune response. This occurs due to the decreased mobilization of polymorphonuclear leukocytes, chemotaxis, phagocytic activity, lower secretion of cytokines such in response to lipopolysaccharides, inhibition of Tumor Necrosis Alpha (TNFα) activity of T-cells, and glycation of immunoglobulin [63].

For treatment of patients with both diabetes and COVID-19, HCQ is suggested because it is safe in diabetes, and was useful for COVID-19 patients [64,42]. It can be administered with zinc supplements to enhance the clinical efficacy [65]. A retrospective analysis showed reduced rates of death and intubation in patients with viral pneumonia who were continued on ACE inhibitors [66]. But theoretically, it could increase the risk of infection with COVID-19, especially for diabetic patients [67]. In a case-report study on a patient with both COVID-19 and diabetes, the patient was discharged from the hospital after 15 days. In this case, the doctors administered antibiotics (meropenem, linezolid) and antiviral agents (ganciclovir, oseltamivir) [17]. Other studies provided further suggestions – for instance, that a patient with diabetes should follow blood-glucose levels and increase hygienic standards [21,40]. Furthermore, remote monitoring systems and in-home visits, the usage of social media accounts, and reducing hospital referrals, have also been suggested as effective and health care systems are encouraged to follow these suggestions [18,41,43]. The IDF has suggested a guide for diabetics that includes similar general guidelines for others [49]. The importance of these suggestions has been especially highlighted for developing countries.

Based on the findings, diabetes should be considered as a risk factor for the severity of symptoms of COVID-19, and the best function is reducing the expose to corona sources.

Health systems must create programs aiming to reduce exposure and the risk of disease in diabetes patients. Further study must be conducted for more information.

4.1. *Limitations*

In this study, we maintained a comprehensive search strategy by key review tasks that included all the studies assessed both diabetes and COVID-19. However, even though we had no publication bias; it is possible that we missed an unpublished data, because we did not search the grey literature. Some of the included studies were case-studies/case series and we included them because not enough research has been done so far. In addition, there were a bias in examined population, which is understandable due to that the disease outbreak came from Asian population.

4.2. *Implications and recommendations*

This study has implications for clinical practice and further studies.

More complete reports about patients with both diabetes and COVID-19 are needed. For further studies, other populations except China should be considered to get a conclusive estimate of the condition of patients around the world.

5. Conclusion

Diabetes and COVID-19 are heath treated conditions that spread in whole of the world. Diabetes patients are more of other people in danger of severity of COVID-19 and mortality, and consisted of 14.5% of COVID-19 patients. Best function is prevention and then usage of evidence-based treatments. For this reason, our suggestions include:

For prevention:

1. Launch remote control systems and faraway learning (telemedicine, social media account)
2. Limit the use of gliptin drugs
3. Blood glucose must be controlled
4. Limit the use of ACEI drugs
5. Reduce unnecessary hospital admissions
6. Attention to nutrition
7. Regard to the guidelines of the country's health-care system in preventing of infection

After infection:

1. Monitoring the symptoms and rapid referral
2. Monitoring the blood glucose
3. Monitoring for AKI complication
4. Monitoring for ARDS
5. Use of hydroxychloroquine
6. Reduction of adverse drug reactions
7. Attention to nutrition (hydration, protein, and etc.)
8. Long-time follow-up

Key Summary Points

Why carry out this study? COVID-19 pneumonia is a newly recognized illness and causes many disability and death. specially in diabetes patients, is important because of suggested as a risk factor which contributes to the severity and mortality of COVID-19. to date, there are no comprehensive studies aiming to explain the exact relationship between diabetes and COVID-19.

What was found in this study?

There were no differences in symptoms between patients who suffered from both diabetes and COVID-19 and other patients.
Prevalence of diabetes in COVID-19 patients was 14.5%.
Severe symptoms and the death rate is higher among patients with both diabetes and COVID-19
We suggested some therapeutic consideration to diabetic patients with coronavirus
We suggested some advices for diabetic patients in outbreak of COVID-19

Declarations

Consent to publish

No applicable.

Availability of data and materials

Data are in references studies.

Authors' contributions

MJ and AB contributed in designing the study. MJ, AB and PAS contribute in initial search and data extraction. The final report and manuscript were written by MJ, AB, ZV and PAS.

All authors contributed to drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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