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Review

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

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\textbf{A B S T R A C T}

\textbf{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.

\textbf{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.

\textbf{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.

\textbf{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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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 betacoronavirus [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 coronavirus. 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 suggest 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 type 2 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-
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 |
|---------------------------------------------------------------------------------------|------|------------------------------------------------------------------------|--------------|
| Shi et al. [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 timepoints throughout the disease course | Retro        |
| Zhao et al. [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 al. [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 | Retro        |
| Xu et al. [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 al. [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 al. [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 al. [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 al. [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 | Retro        |
| Yang et al. [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        |
| Authors               | Year | Title                                                                                   | Journal                    | Type          |
|----------------------|------|-----------------------------------------------------------------------------------------|----------------------------|---------------|
| Zhou et al. [21]     | 2020 | Assessment of blood glucose management in diabetic patients                               | Diabetes Research and Clinical Practice | Retro         |
| Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China; *Metabolism Clinical and Experimental* |      | Investigate the clinical characteristic and allergy status of patients infected with SARS-CoV-2 | Allergy        | Retro         |
| Zhang et al. [10]    | 2020 | Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China; *Allergy* | *Clinical and Experimental* | Review        |
| Zhou et al. [31]     | 2020 | Risk factors for mortality and a detailed clinical course of illness, including viral shedding in COVID-19 patients | The Lancet                 | Retro         |
| Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study; *The Lancet* |      | To investigate the characteristics and prognostic factors in the elderly patients with COVID-19 | *Allergy*     | Retro         |
| Wang et al. [32]     | 2020 | Blood glucose management for the outbreak of 2019 novel coronavirus disease               | *The Lancet*               | Review        |
| Coronavirus Disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up *Journal of Infection* |      | To describe the epidemiological and clinical characteristics of novel coronavirus (2019-nCoV)-infected pneumonia | *Clinical and Experimental* | Retro         |
| Wang et al. [40]     | 2020 | Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed; *Diabetes Research and Clinical Practice* | *Clinical and Experimental* | Review        |
| Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China; *JAMA* |      | Describe the clinical characteristics and outcomes in patients with COVID-19 pneumonia who developed acute respiratory distress syndrome (ARDS) or died | *Clinical and Experimental* | Retro         |
| Wu et al. [34]       | 2020 | To provide the international community with a deeper understanding of COVID-19            | *Clinical and Experimental* | Case-series   |
| Clinical Features and Treatment of COVID-19 Patients in Northeast Chongqing; *Medical Virology* |      |                                                                                         |               |               |
| Authors | Title | Year | Summary |
|---------|-------|------|---------|
| Bhatraju et al. [37] | Covid-19 in Critically Ill Patients in the Seattle Region — Case Series | 2020 | Describe the demographic characteristics, coexisting conditions, imaging findings, and outcomes among critically ill patients with Covid-19. |
| Rogers et al. [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; | 2020 | Reduce the burden on the healthcare system by keeping diabetic foot and wound patients safe, functional, and at home. |
| Li et al. [38] | Clinical characteristics of 25 death cases with COVID-19: a retrospective review of medical records in a single medical center, Wuhan, China; | 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. |
| Hui et al. [22] | Clinical and radiographic features of cardiac injury in patients with 2019 novel coronavirus pneumonia; | 2020 | Investigate the correlation between clinical characteristics and cardiac injury of COVID-19 pneumonia. |
| Chen et al. [27] | Hypertension and Diabetes Delay the Viral Clearance in COVID-19 Patients; | 2020 | Detect the underlying diseases that could impact on viral clearance. |
| Han et al. [17] | A Diabetic Patient with 2019-nCoV (COVID-19) Infection Who Recovered and Was Discharged from Hospital; | 2020 | Report a patient with both diabetes and COVID-19. |
| Iacobucci et al. [41] | Covid-19: diabetes clinicians set up social media account to help alleviate patients’ fears; | 2020 | Set up a social media account to help alleviate patients’ fears around covid-19 and provide them with “a secure base” of information. |
| Singh et al. [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; | 2020 | Review existing literature and relevant websites regarding Chloroquine and hydroxychloroquine and COVID-19, adverse effects related to drugs, and related guidelines. |
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 suggest 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 type 2 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,
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%)
| Study                  | Treatment/Suggestion                                                                 |
|------------------------|---------------------------------------------------------------------------------------|
| Zhou et al. [21]       | 1. Management of blood glucose                                                       |
| Wang et al. [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 al. [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 al. [17]        | 1. Symptomatic treatment                                                             |
|                        | 2. Antibiotics (meropenem, linezolid)                                                |
|                        | 3. Antiviral agents (ganciclovir, oseltamivir)                                       |
| Iacobucci et al. [41]  | 1. Social media account                                                              |
| Singh et al. [42]      | 1. Use of hydroxychloroquine (HCQ)                                                   |
| Gupta et al. [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 vaccinations                                           |
|                        | **General 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 areas                                           |
|                        | **Measures 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 |
Diabetes is one of the most common diseases, and the leading risk factor for poor outcomes and complications such as ARDS and even death. Hu reported that diabetes is more likely than healthy people to develop COVID-19 disease and complications [51]. This result needs further investigation.

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 related with ARDS and prolonged cure in COVID-19 patients [32]. 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].

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 (TNFs) 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 – for instance, that a patient with diabetes should reduce the exposure 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 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 health 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 (telmedicine, 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

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