






Impact of Covid-19 on diabetic adults: systematic review

Impacto da Covid-19 em adultos diabéticos: revisão sistemática

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Abstract

Aim: to identify which complications and prognosis of diabetic patients, hospitalized, who acquired COVID-19, through a systematic review. **Methods:** a systematic review based on the PRISMA flowchart, including cohort studies, available in Portuguese, English, Spanish, French, and Mandarin, published from 2019 to 2020, using the PICOS strategy, in the databases: PubMed, Web of Science, Scielo, Lilacs, Scopus and Science Direct, which in addition to the inclusion criteria after questionnaires to assess methodological quality and risk of bias. **Results:** of the 811 articles researched, 6 were included in this research. These studies showed that patients with COVID-19 and higher DM with worse prognosis, spent more time in the ICU, constantly needed indifference, greater complications when related to other comorbidities, high mortality rate, and glycemic control associated with advanced age directly affected patients. Outcomes even of non-diabetic subjects. **Conclusion:** this review identified the severity of the pathophysiological association is related to older age and biochemical and inflammatory factors linked to the two pathogens and that these subjects are more prone to specialized hospital care, which, however, result in high rates of hospital mortality.

Keywords: Diabetes Complications; Diabetes; COVID-19; SARS-CoV-2; Coronavirus Infections.

Resumo

Objetivo: identificar quais complicações e prognósticos dos pacientes diabéticos, internados, que adquiriram COVID-19, por meio de uma revisão sistemática. **Métodos:** foi realizada uma revisão sistemática baseada no fluxograma PRISMA, incluindo estudos de coorte, disponíveis em português, inglês, espanhol, francês e mandarim, publicados de 2019 a 2020, utilizando a estratégia PICOS, nas bases de dados: PubMed, Web of Science, Scielo, Lilacs, Scopus e Sciece Direct. Além dos critérios de inclusão passam por questionários para avaliar a qualidade metodológica e risco de viés. **Resultados:** dos 811 artigos pesquisados, 6 foram incluídos nesta pesquisa. Esses estudos mostraram que pacientes com COVID-19 e DM apresentam pior prognóstico, maior permanência em UTI, necessidade constante de ventilação invasiva, maiores complicações quando relacionadas a outras comorbidades, elevado índice de mortalidade, e o controle glicêmico associado à idade avançada afetavam diretamente os desfechos inclusive de pacientes não diabéticos. **Conclusão:** esta revisão identificou que a gravidade da associação fisiopatológica está relacionada à idade mais avançada e aos fatores bioquímicos e inflamatórios ligados aos dois patógenos e que esses sujeitos são mais propensos ao atendimento hospitalar especializado, o que, no entanto, resulta em altas taxas de mortalidade hospitalar.

Palavras-chave: Complicações do Diabetes; Diabetes; COVID-19; SARS-CoV-2; Infecções por Coronavírus.

INTRODUCTION

In December 2019, several individuals were admitted to Chinese hospitals with an initial diagnosis of pneumonia of etiology and after studies, the etiological agent of the disease was identified and named as the new coronavirus (COVID-2019). Soon after, the World Health Organization (WHO) defined this condition as the Severe Coronavirus Acute Respiratory Syndrome (SARS-CoV) that caused the pandemic, in addition to pointing out that the pathogen acted, above all, in the cardiorespiratory system¹.

With this, several researchers have started studies that have shown that pre-existing comorbidities can be a significantly increased risk factor for the development of COVID-19², and among these diseases, Diabetes Mellitus (DM) stands out, which

is subdivided into type 1, which generally leads to absolute insulin deficiency, due to low production, due to autoimmune destruction of pancreatic β cells; and type 2, in which there is a relative deficiency due to peripheral insulin resistance³.

In addition to having a high worldwide prevalence with estimates of growth in the coming decades, DM is more complex than imagined. This is because its decompensation can lead to greater susceptibility to infections, which makes its carriers part of the so-called risk groups, a factor that is worrying with the advance of the coronavirus pandemic^{4,5}.

Based on the above, many scientists have carried out numerous

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Conflict of interest: The authors declare that there is no conflict of interest.

Received: 2022 Jan 11; Revised: 2022 Mar 3; Accepted: 2022 Mar 7

2 Impact of covid-19 on diabetic adults: systematic review

researches, intending to discover new treatments, as well as the causes and consequences resulting from the high transmissivity and virulence of COVID-19 for certain parts of the population, for those considered at-risk groups, as is the case with diabetics. Therefore, the objective was to identify which complications and prognosis existed at that time, as well as the mortality rate concerning diabetics who acquired COVID-19 and were hospitalized, through a systematic review.

METHODS

Study design

A systematic review (SR) from the flowchart of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), including case-control and cohort studies. We stress that studies of the Randomized Clinical Trial type were not part of this SR as they were not found at the time the research was conducted. This protocol was registered in the International Prospective Register of Systematic Review (PROSPERO) network under registration number CRD42020190510.

Inclusion criteria

Open access scientific articles, with adult participants, who are diagnosed with diabetes and have COVID-19, with texts available in Portuguese, English, Spanish, French, and Mandarin published in 2019 and 2020. This period was determined, due to the increase in demand for research on COVID-19 and the correlation with chronic diseases such as diabetes mellitus.

Exclusion criteria

Duplicate articles, articles in which the title did not include the terms COVID-19 and Diabetes or their synonyms, articles with incomplete title and/or abstract, and Gestational diabetes were excluded.

Study protocol

Search strategy

The PICOS strategy guided the elaboration of the guiding question of RS. Thus, the delimited research question was: "what complications and prognosis exist in diabetic patients who acquired COVID-19?". The search strategy used is as follows: (Coronavirus OR 2019-nCoV OR "Coronavirus infections" OR COVID-19 OR "Global health emergency" OR SARS-CoV-2) AND ("Diabetes mellitus" OR "Diabetes Complications" OR "Diabetes type 1" OR "Diabetes type 2"). Searches were performed in the following databases: Web of Science, PubMed / Medline (National Library of Medicine), SciELO (Scientific Electronic Library Online), LILACS (Latin American and Caribbean Health Science Literature Database), Scopus, Science direct. Case-control and cohort studies from 2019 to 2020 were considered for inclusion. The specific elements of the PICOS strategy and the search strategy used in each database are described in Figure 1.

Figure 1. A: Elements of the PICO strategy, descriptors, and keywords, Brazil, 2020.

B: Search strategies used in the databases, Brazil, 2019 - 2020.

| Component | Definition | Descriptors | Keywords |
|---------------------------|--|----------------------------------|--|
| P: Population of interest | Individuals with diabetes and COVID-19 | Diabetes mellitus Coronavirus | Diabetes Complications Diabetes type 1 Diabetes type 2 COVID-19 SARS-CoV-2 2019-nCoV Coronavirus infections Global health emergency |
| I: Intervention | - | - | - |
| C: Comparison | - | - | - |
| O: Outcome | Complications and prognosis in diabetic patients who acquired COVID-19 | - | - |

| Data base | Search strategies |
|------------------------|---|
| Online library | |
| Web of science | TOPIC: ((Coronavirus OR 2019-nCoV OR "Coronavirus infections" OR COVID-19 OR "Global health emergency" OR SARS-CoV-2) AND TÓPICO: (("Diabetes mellitus" OR "Diabetes Complications" OR "Diabetes type 1" OR "Diabetes type 2")) Filter: Year (2019-2020); type of document (article); languages (English) |
| Pubmed | (Coronavirus OR 2019-nCoV OR "Coronavirus infections" OR COVID-19 OR "Global health emergency" OR SARS-CoV-2) AND ("Diabetes mellitus" OR "Diabetes Complications" OR "Diabetes type 1" OR "Diabetes type 2") Filter: Year (2019-2020); Full text; languages (Chinese, English, French, Portuguese, Spanish) |
| SciELO (via sciELO.br) | (Coronavirus OR 2019-nCoV OR "Coronavirus infections" OR COVID-19 OR "Global health emergency" OR SARS-CoV-2) AND ("Diabetes mellitus" OR "Diabetes Complications" OR "Diabetes type 1" OR "Diabetes type 2") Filter: Year (2019-2020); type of document (article); languages (Spanish, English and Portuguese) |
| LILACS | (Coronavirus OR 2019-nCoV OR "Coronavirus infections" OR COVID-19 OR "Global health emergency" OR SARS-CoV-2) [Palavras] and (Diabetes Complications or Diabetes type 1 or Diabetes type 2) [Palavras] |
| Scopus | TITLE-ABS-KEY ((coronavirus OR 2019-ncov OR "Coronavirus infections" OR covid-19 OR "Global health emergency" OR sars-cov-2) AND ("Diabetes mellitus" OR "Diabetes Complications" OR "Diabetes type 1 " OR "Diabetes type 2")) AND DOCTYPE (ar) AND PUBYEAR > 2018 Filter: Filter: Year (2019-2020); type of document (article); type of access (all); languages (English, Spanish, Chinese, French, Portuguese) |
| Science direct | (Coronavirus OR 2019-nCoV OR "Coronavirus infections" OR COVID-19 OR SARS-CoV-2) AND ("Diabetes mellitus" OR "Diabetes Complications" OR "Diabetes type 1" OR "Diabetes type 2") Filter: Year (2019-2020); Research articles |

Selection of articles

To assist in conducting this study, the Parsifal software was used, which is an online tool designed to help researchers manage systematic reviews. Initially, the title analysis was carried out, followed by the reading of the abstracts to identify those that would be evaluated in full, independently, by four researchers. The final necessary data were extracted using an instrument containing identification data (authors and year), objective, study design, population characteristics (sample size, average age, gender, type of DM), and existing complications in these patients.

Assessment of methodological quality of studies and risk of bias

To assess methodological quality, the instrument Scottish Intercollegiate Guidelines Network (SIGN 50) was used, which consists of a form designed to identify whether articles are of high, acceptable, low quality or whether they will be rejected.

3 Impact of covid-19 on diabetic adults: systematic review

For each study, the corresponding questionnaire was used, with approximately 12 items each and divided into two phases, the first of which included themes such as the question addressed in the research, comparison between groups and measures for investigating cases (case-control); percentage of individuals recruited, evaluation of results, main potential confounders and provision of confidence intervals (cohort). In the second phase of both questionnaires, the researchers made a subjective reassessment and decided on the qualification of the article and its classification in the research^{6,7}.

Another tool used to assess the risk of study bias was A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies (ACROBAT-NRSI), which consists of a scale that classifies the article as low risk, moderate risk, severe risk, and critical risk of bias. In this way, it follows seven domains: confusion,

selection of study target participants, measurement of interventions, deviations from intended interventions, lack of data, measurement of results, and selection of the reported result⁸. For this purpose, four authors performed both assessments independently and if there were differences, a fifth assessor would be asked to perform the analysis blindly and make a group decision based on majority votes.

Analysis of results

After reading the articles in full, the reviewers filled out a data extraction instrument containing information about: authors and year; objective; study design; population characteristics (sample size, average age, gender, type of DM); and complications existing in these diabetic patients who contracted COVID-19. Based on these data, a descriptive analysis of the results was performed, and this information is presented in Table 1.

Table 1. Characteristics of studies on the complications of COVID-19 in diabetics, Brazil, 2020.

| Author and year | Diabetes type by group | Complications identified | Mortality |
|--------------------|---|--|---|
| Zhu et al., 2020 | G1 (810): G1-I (282) - controlled BG; G1-II (528) - patients with DM2 uncontrolled (subdivide into two groups with 250 of each); G2: 6385 non-diabetics with Covid-19. | Higher incidences of fatigue, dyspnea, and bilateral lung injury, as well as lymphopenia, increased production of leukocytes, elevated inflammatory markers, decreased renal function, increased coagulation, and saturation less than 95%. In addition to a higher occurrence of ARDS, acute cardiac injury, acute kidney injury, septic shock, and disseminated intravascular coagulation with diabetic groups compared to non-diabetics. | The in-hospital mortality rate was higher in DM2 patients with a crude HR equal to 2.90. Even with more aggressive treatment against COVID-19 and comorbidities, the diabetic group had decreased lymphocyte count and increased neutrophil count added to higher levels of serum IL-6, CRP, and LDH, and higher levels of BG. BG level was associated with comorbid hypertension, CHD, as incidences of decreased lymphocyte count and elevated neutrophil count, and serum CRP and creatinine levels. |
| Chung et al., 2020 | G1 (29): G1-I (18, <70 years old) - Patients with Covid-19 and DM2 and CAD; G1-II (11, > or = 70 years) - Patients with Covid-19 and DM2 and CAD; G2 (81): patients with Covid-19 without DM2. | Systolic and diastolic blood pressures were higher, had higher leukocyte counts, neutrophil counts, lactate dehydrogenase, serum glucose and C-reactive protein levels, and lower albumin levels in patients with DM. | Rates of progression to SCO were significantly higher in patients aged ≥70 years, with the outcomes being: composite SDRA, septic shock, ICU, and 28-day mortality. |
| Ren et al., 2020 | G1 (89): mild cases of Covid-19 with 16 with DM2; G2 (62): severe cases Covid-19 with 23 with DM2. | The TyG index was higher in severe cases; patients in the highest tertile of TyG had higher levels of WBC, NEU, AST, LDH, CRP, and ferritin, but lower levels of lymphocyte counts; those with an increasing level of the TyG index had a higher incidence of severe cases and death. | The TyG index was a risk factor for increased mortality and causes of death ranged from respiratory failure, heart failure, inflammatory storm, sepsis, disseminated intravascular coagulation, multiple organ failure, acute kidney injury, malignant arrhythmia, diabetic ketoacidosis, even death sudden and other uncertain events. |
| Yan et al., 2020 | G1 (48): Patients with Covid-19 and with DM1 e DM2; G2 (145): Patients with Covid-19 without DM. Dentre os que tiveram Covid grave (193): S (9) - Surviving and NS (39) - Non-surviving. | More patients with diabetes were admitted to the ICU and received mechanical ventilation treatment; also had a shorter length of hospital stay with higher mortality, and they also had higher levels of total bilirubin. | The median duration of survival from the onset of symptoms was 21 days in patients with DM and 28 days in patients without DM. The median duration of survival since hospital admission was 10 days in patients with DM and 18 days in patients without. |

| Author and year | Diabetes type by group | Complications identified | Mortality |
|--------------------|--|---|--|
| Wu et al., 2020 | G1 (1690): Non-critical patients, in which 206 were diabetics; G2 (697): Critical patients, in which 126 were diabetics. | Admission GS level was an independent risk factor for progression to critical cases/death and the highest median hospital glucose level was independently associated with the highest rate of progression to critical cases/death among non-critical cases. | The mean hospital stay was 15.8 days and the 30-day mortality was 14.6% for all patients and 30.9% for critical cases. |
| Zhang et al., 2020 | G1 (84) patients without a history of DM; G2 (21): patients with secondary hyperglycemia; G3 (61): patients with DM. | Diabetic patients were more likely to develop severe or critically ill subtypes with more complications such as acute respiratory distress, acute heart injury, and had more use of antibiotic therapy, noninvasive and invasive mechanical ventilation, in addition to a higher median WBC count and count. neutrophil median. | The fatality rate was higher in diabetics and the highest level of FBG on admission was an independent predictor of death. |

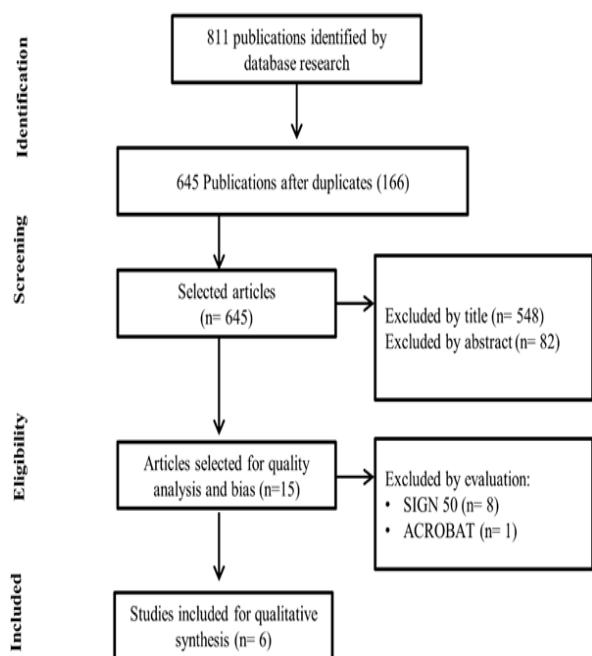
Subtitle: G1: Group one; G2: Group two; G3: Group three; G1-I: Subgroup one, G1-II: Subgroup two; Blood glucose (mmol/L); ARDS: Acute respiratory distress syndrome; DM2: Type 2 diabetes mellitus; HR: Heart rate (bpm); IL-6: Interleukin 6; CRP: C-reactive protein; LDH: Lactate dehydrogenase; CHD: Coronary heart disease; CAD: Coronary artery disease; SCO: Severe and critical outcome; SDRA: Acute respiratory distress syndrome; ICU: Intensive care unit; TyG: Triglyceride-glucose index; WBC: White blood cells; NEU: Neutrophil count; AST: Aspartate transaminase; DM1: Type 1 diabetes mellitus; DM: Diabetes mellitus; GS: Blood glucose; FBG: Fasting blood glucose.

RESULTS

Inclusion of studies

After applying the search strategies on a scientific basis, 811 studies were identified, of which 6 were included and integrated into this SR. After performing the inter-rater Kappa test, the agreement was 85%, Kappa value of 0.85, and value p = 0.001. The flowchart-based on the PRISMA recommendation⁹ is shown in figure 2.

Figure 2. Flowchart of the study selection process, Brazil, 2020



Subtitle: SIGN 50, Scottish Intercollegiate Guidelines Network; ACROBAT-NRSI, A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies.

Quality of studies

Of the 15 articles selected for evaluation¹⁰⁻²⁴, only seven were approved by SIGN 50, as they were considered acceptable and were in line with the objectives of this review. Subsequently, they went through ACROBAT - NRSI, with only one being excluded for having a serious risk of bias¹³, as shown in figure 3.

Figure 3. Methodological quality and risk of bias, Brazil, 2020.

| SIGN 50 | |
|---------------------|--------|
| AUTHORS | RESULT |
| ZHU <i>et al.</i> | Accept |
| CHUNG <i>et al.</i> | Accept |
| REN <i>et al.</i> | Accept |
| YAN <i>et al.</i> | Accept |
| WU <i>et al.</i> | Accept |
| ZHANG <i>et al.</i> | Accept |
| LI <i>et al.</i> | Accept |

| ACROBAT | | | | | | | | | |
|---------|---------------------|-------------------|-------------------|-----------------|-------------------|----------------------|----------------------------|--|--------------------|
| B | AUTHORS | Bias of confusion | Bias of selection | Bias of gauging | Bias of follow-up | Bias of dice missing | Bias of measure of outcome | Bias of report selective From outcomes | Risk of total bias |
| | ZHU <i>et al.</i> | Moderate | Low | Moderate | NI | Low | Moderate | Low | Moderate |
| | CHUNG <i>et al.</i> | Moderate | Low | Moderate | NI | Low | Moderate | Low | Moderate |
| | REN <i>et al.</i> | Moderate | Low | Moderate | NI | Low | Moderate | Low | Moderate |
| | YAN <i>et al.</i> | Moderate | Low | Moderate | NI | Low | Low | Low | Moderate |
| | WU <i>et al.</i> | Moderate | Low | Moderate | NI | Low | Moderate | Low | Moderate |
| | ZHANG <i>et al.</i> | Moderate | Low | Moderate | NI | Low | Moderate | Low | Moderate |
| | LI <i>et al.</i> | Serious | Serious | Moderate | NI | Low | Moderate | Low | Serious |

Subtitle: A = Evaluation by SIGN 50; B = Evaluation by ACROBAT; NI = No Information.

General characteristics and outcomes

Most of the studies (n = 5) were carried out in China [20–24] and only one in South Korea¹², all retrospective, being four unicentric and two multicentric^{20,23}. The final sample of participating participants ranged from 110 to 7337, and the average age was 53 to 64 years. Table 1 presents the main characteristics and results of the articles included.

Patients with diabetes were more likely to develop serious or critical illnesses with complications, including acute respiratory distress, ARDS, septic shock, ICU care (using invasive and non-invasive mechanical ventilation), acute cardiac injury, and antibiotic therapy^{11,15–17}; being that the systolic and diastolic blood pressure in them were higher^{15,16}, and most studies confirm that diabetic patients tend to have the highest rate of mortality^{11,15,16,18}, this due to the increase of the blood glucose index^{17,19}.

These patients had the values of blood glucose, lymphopenia, leukocytes, neutrophils, serum markers (indicating inflammation), lactic dehydrogenase (LD), aspartate transaminase (AST), highly sensitive C-reaction protein (hsCRP), and coagulation status (dimer D) at high levels^{15–18}, they also received more intensive treatment with a greater need for antibiotics, antifungals, systemic corticosteroids, immunoglobulins, antihypertensives and even vasoactive drugs¹⁶. In addition, there was a need for higher oxygen rates, and non-invasive ventilation (NIV) and invasive ventilation (IV) were also applied more frequently^{15–17}.

In these studies, there were mainly male participants, and hypertension was the most prevalent comorbidity^{12,20–24}, but others were also observed, such as cardiovascular disorders (acute myocardial infarction, coronary syndrome, heart failure), cerebrovascular and chronic kidney disease (CKD)^{20–22,24}. In addition, fever, cough, dyspnea, and fatigue were the most common symptoms in both groups (with and without DM)^{20–22,24}, although diabetics report a higher incidence of fatigue and dyspnea^{15,20}.

DISCUSSION

Unanimously, the results found in the included articles point out that in hospitalized patients, those who are diabetics and are symptomatically diagnosed with COVID-19 have a higher risk of admission to the intensive care unit and need mechanical ventilation. In this context, the mortality outcomes are also more expressive in these patients when compared to non-diabetic patients with a positive diagnosis of COVID-19.

The pathophysiological association between DM and COVID-19 is not fully understood, however, it is known that both pathologies have a significant inflammatory effect, with this, evidence is being constructed to suggest a potential pathophysiological aspect for systemic diseases and inflammation in metabolic syndromes, to explain the disproportionate effect of COVID-19

in diabetic patients²⁵.

Another important aspect to be considered for the effects of COVID-19 in diabetic patients is that individuals with metabolic syndromes, in general, have impaired immune functions, with this, the complications of DM can have a synergistic role in the pathogenesis of the form more severe of COVID-19, which includes ARDS, making patients more susceptible to death from respiratory failure associated with systemic inflammation, regardless of viral load^{26–28}.

Regarding the cardiovascular and metabolic diseases of COVID-19 individuals, a meta-analysis concluded that Systemic Arterial Hypertension (SAH) is the pathogenesis with the highest prevalence, followed by cerebrovascular disease (CVD) and then DM²⁹. As for symptomatology, a prospective study of diabetic patients infected with COVID-19 in hospitals in the United Kingdom shows that the most common symptoms are cough, fever, and shortness of breath³⁰.

In addition, patients with DM and COVID-19 have a higher risk of progression to severe conditions, especially in the elderly with a long history of diabetic complications, these factors provide these patients with greater chances of entering the ICU and admitting MV³¹. In a robust cohort study - published after selecting articles for this review - it was found that the majority of patients included were men (53.4%), with a mean age of 57 years (46-67)³².

In the biochemical analysis, it is noted that inflammatory processes linked to blood hyperglycemia are impaired due to dysfunctions of cells such as monocytes/macrophages, dendritic cells, natural killers' cells, lymphocytes, and cytokines²⁷. Concomitantly, COVID-19 in its most severe form is associated with systemic inflammation³³. Furthermore, uncontrolled hyperglycemia, even in non-diabetic patients, is associated with increased severity and mortality in patients with COVID-19³⁴.

Therefore, it is noted that laboratory findings, of diabetics with COVID-19, have reduced values of lymphocytes, uric acid, and albumin and increased levels of CRP compared with groups of patients with COVID-19 without DM. The decrease in uric acid and albumin levels may be associated with the response to oxidative stress and nutritional consumption, the decrease in lymphocytes, and the increase in CRP may be related to infection³⁵.

Regarding TyG levels, the literature has already pointed out the link between increased rates and the development of DM, since TyG indices are highly associated with the risk of DM and are also an important biomarker for the development of metabolic syndromes³⁶. Other studies have also shown that the high level of TyG is also a high risk for cardiovascular disease, including coronary artery disease (CAD) and ischemic stroke³⁷.

Given these pathophysiological characteristics between the two pathologies, the importance of a careful look by

6 Impact of covid-19 on diabetic adults: systematic review

health professionals for patients with pre-existing diabetes is highlighted, as this condition is significantly associated with a two to three times greater risk of a serious condition, with admission in ICU, and hospital mortality associated with COVID-19³⁸.

In this context, from a therapeutic point of view, several studies provide more robust evidence on how endocrine drug interventions can influence more satisfactory clinical results between the two associated diseases, research in this area is urgently needed for a better understanding of possible changes in genetic predispositions between populations, the exact pathophysiological mode between COVID-19 and diabetes, followed by its clinical management³⁹.

With the present study, it is concluded that DM is an important comorbidity in the nosological condition of individuals with COVID-19, especially in patients with uncontrolled hyperglycemia, thus, the severity of the pathophysiological

association is associated with older age and with biochemical and inflammatory factors linked to the two pathogens. Therefore, it is also understood that diabetic individuals with COVID-19 have a higher propensity for hospital care, including admission to the ICU and admission of MV, in addition to higher rates of hospital mortality.

This SR has some limitations, although the articles included for the final results have at least a moderate methodological quality after undergoing a rigorous evaluation, it is known that due to the high demand for studies on the subject and the consequent update of new publications about COVID-19, possibly new studies of good quality and low risk of bias could not be analyzed and included in the results of this review. Furthermore, it should be noted that the cohort studies included were all retrospective, thus, it is understood that these studies may generate a confounding bias regarding the exposure of the groups due to the absence of a prospective follow-up of the patients and possible changes in the outcomes.

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7 Impact of covid-19 on diabetic adults: systematic review

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Como citar este artigo/ How to cite this article:

Alves BLS, Montelo ES, Lima LB, Melo ACS, Gouveia GPM. Impact of covid-19 on diabetic adults: systematic review. *J Health Biol Sci*. 2022; 10(1):1-7.