

MORTALITY IN PATIENTS WITH DIABETES BY COVID 19 A SYSTEMATIC REVIEW**Mortalidade em pacientes com diabetes por covid 19 uma revisão sistemática**

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Abstract

The objective was to carry out a systematic review of what has been published so far on mortality in patients with COVID-19 associated with diabetes comorbidity. A search was carried out in PubMed, Ovid MEDLINE, EMBASE and EMBASE Classic and Google Scholar databases; up to April 2020 using the search medical subheading (MeSH) terms: "mortality from Coronavirus", "mortality from COVID-19" and "mortality in patients with diabetes by COVID-19". Enrolled studies were assessed independently by two blinded researchers. Studies quality was assessed using the Jadad scale. The articles score equal to or greater than two points were considered high methodological quality. Initially, 65 articles were found and 46 were excluded for not meeting the eligibility criteria. Among the 10 remaining, 3 were excluded because they had a Jadad score lower than two points. Among the remaining seven, two were excluded because they were meta-analysis. Eventually, five articles remained for final analysis. For all, mortality among patients with diabetes was higher than without it. The risk of global mortality among diabetic patients was 8.9 times higher ($p < 0.0001$) than the ones without diabetes. The time of diagnosis could be more determining for mortality, meanwhile Hb1Ac level was not determining. It is concluded that the mortality risk observed by COVID-19 is higher among diabetic patients than healthy age matched peers. This result can be partially explained by hormonal signaling changes, such as blood clotting and abnormal pancreas functioning.

Keywords: diabetes, SARS-CoV-2, COVID 19, Mortality.

Resumo

Objetivou-se realizar uma revisão sistemática do que foi publicado até o momento sobre mortalidade em pacientes com COVID-19 associada à comorbidade diabética. Métodos: Foi realizada uma busca nas bases de dados PubMed, Ovid MEDLINE, EMBASE e EMBASE Classic e Google Scholar; até abril de 2020 usando os termos de pesquisa do subtítulo médico (MeSH): "mortalidade por Coronavirus", "mortalidade por COVID-19" e "mortalidade em pacientes com diabetes por COVID-19". Os estudos inscritos foram avaliados de forma independente por dois pesquisadores cegos. A qualidade dos estudos foi avaliada por meio da escala de Jadad. Os artigos com pontuação igual ou superior a dois pontos foram considerados de alta qualidade metodológica. Resultados: Inicialmente, foram encontrados 65 artigos e 46 foram excluídos por não atenderem aos critérios de elegibilidade. Dos 10 restantes, 3 foram excluídos por apresentarem escore Jadad inferior a dois pontos. Entre os sete restantes, dois foram excluídos por serem meta-análises. Por fim, restaram cinco artigos para análise final. Para todos, a mortalidade entre os pacientes com diabetes foi maior do que sem ele. O risco de mortalidade global entre os diabéticos foi 8,9 vezes maior ($p < 0,0001$) do que os sem diabetes. O momento do diagnóstico pode ser mais determinante para a mortalidade, enquanto o nível de Hb1Ac não foi determinante. Conclui-se que o risco de mortalidade observado pelo COVID-19 é maior entre pacientes diabéticos do que entre pares saudáveis da mesma idade. Este resultado pode ser parcialmente explicado por alterações de sinalização hormonal, como coagulação do sangue e funcionamento anormal do pâncreas.

Palavras-chave: diabetes, SARS-CoV-2, COVID 19.

1. Introduction

Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease (COVID-19) and, in severe cases, developing into the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological and clinical characteristics of patients with COVID-19 have been reported, but risk factors for mortality in patients with prior diabetes mellitus comorbidity and a detailed clinical illness course, including viral shedding, have not been well described¹⁻².

On April 7, 2020, the World Health Organization (WHO) reported 2,287,836 confirmed cases of COVID-19 worldwide. Also, 160,323 deaths were reported, 7% death rate worldwide. The United States of America has most of cases with 733,921 and 39,019 deaths (0.053 death rate), followed by Spain with 191,726 cases and 20,043 deaths (0.101 death rate). Surprisingly, Italy does not have as many cases as reported in other countries (175,925 confirmed cases and 23,227 deaths), however, it presents the highest mortality rate (0.132) seen up to this date³.

A retrospective cohort study investigated several risk factors for death in adults with COVID-19⁴. Older age, d-dimer levels greater than 1 µg/mL and higher SOFA score prior to hospital admission were particularly associated with higher chances of in-hospital death. Additionally, elevated levels of blood IL-6, high-sensitivity cardiac troponin I, lactate dehydrogenase and lymphopenia were more commonly seen in severe COVID-19 illness⁴. Similar results have already been shown by other studies⁵⁻⁷.

Although the clinical manifestations of COVID-19 are surrogate of respiratory symptoms^{8,9}, some patients with diabetes commonly develop severe illness¹⁰. In addition, these patients might have increased death risk¹¹. The coronavirus 2019 disease (COVID-19) currently represents a serious public health issue worldwide. As it is well known, patients with diabetes are at higher risk of infection especially during periods of poor glycemic control¹¹. Recent investigations have reported that diabetes mellitus (DM) is one of the most common comorbidity accompanied by the COVID-19 infection¹²⁻¹³. Additionally, some studies have suggested that those subjects seem to have a higher mortality risk during the infection¹⁴⁻¹⁵.

Therefore, understanding the damage caused by SARS-CoV-2 to patients with diabetes, as well as its underlying mechanisms, is of great importance, so that their treatment can be prompt and effective towards mortality reduction. According to this, our study aimed to carry out a systematic review of what has been published so far on mortality from COVID-19 in these patients.

2. Method

This is a systematic review of the literature. Studies search was carried out in the PubMed, Ovid MEDLINE, EMBASE and EMBASE Classic and Google Scholar databases up to April 2020 using the search medical subheading (MeSH) terms: "mortality from coronavirus", "mortality from COVID- 19" and "mortality in patients with diabetes by COVID-19 ". The search was limited to studies written in English. At first, studies analysis, general characteristics of the study sample, and COVID-19 mortality in patients with diabetes were necessary to be reported. Studies published as review articles, letters, case studies, editorials, conference abstracts, family-based studies and articles without abstracts were excluded.

Studies supplied by the database search strategy were assessed independently by two blinded researchers. Study quality was assessed using the Jedad scale¹⁶. This scale has a maximum score of five points, it is subdivided into three topics: randomization, blind and an account of all patients. The score of the articles is, thus, distributed as explained below.

Randomization: 1 point if randomization is mentioned; 1 additional point if the method of randomization was accomplished using a computer-based randomization software, generated appropriately by random number list, coin toss or well-shuffled envelopes. Deduct 1 point if the method of randomization is inappropriate (minimum 0).

Blind: 1 point if blinding is mentioned; 1 additional point if the method blinding is appropriate. Deduct 1 point if the method of blinding is inappropriate (minimum 0).

An account of all patients: 1 point if all patients in the trial are known. If there is no data, the reason is indicated.

Initially, the researchers were trained to standardize the methodological application, which consisted of discussing the Jedad scale items and summarizing the articles; two researchers applied the scale independently and if there were any disagreements between them, they were solved by discussing and reaching a consensus. The articles that obtained a score equal to or greater than two points on the scale were considered as having high methodological quality.

3. Results

Initially, 53 articles were found with the mesh terms "mortality from Coronavirus", "mortality from COVID-19" and "mortality in patients with diabetes by COVID-19". Then a second search round was performed based on the references of the first studies found; 12 additional articles were found, 3 were duplicated. Among the 62 full texts found, 46 were excluded for not meeting the

eligibility criteria (none of those included the mortality rate for patients with diabetes). Among the 10 articles that met the criteria, 3 were excluded because both evaluators rated a Jadad score lower than two points. Among the remaining seven, two were excluded because they were meta-analysis. Final analysis comprised five full text studies (Figure 1).

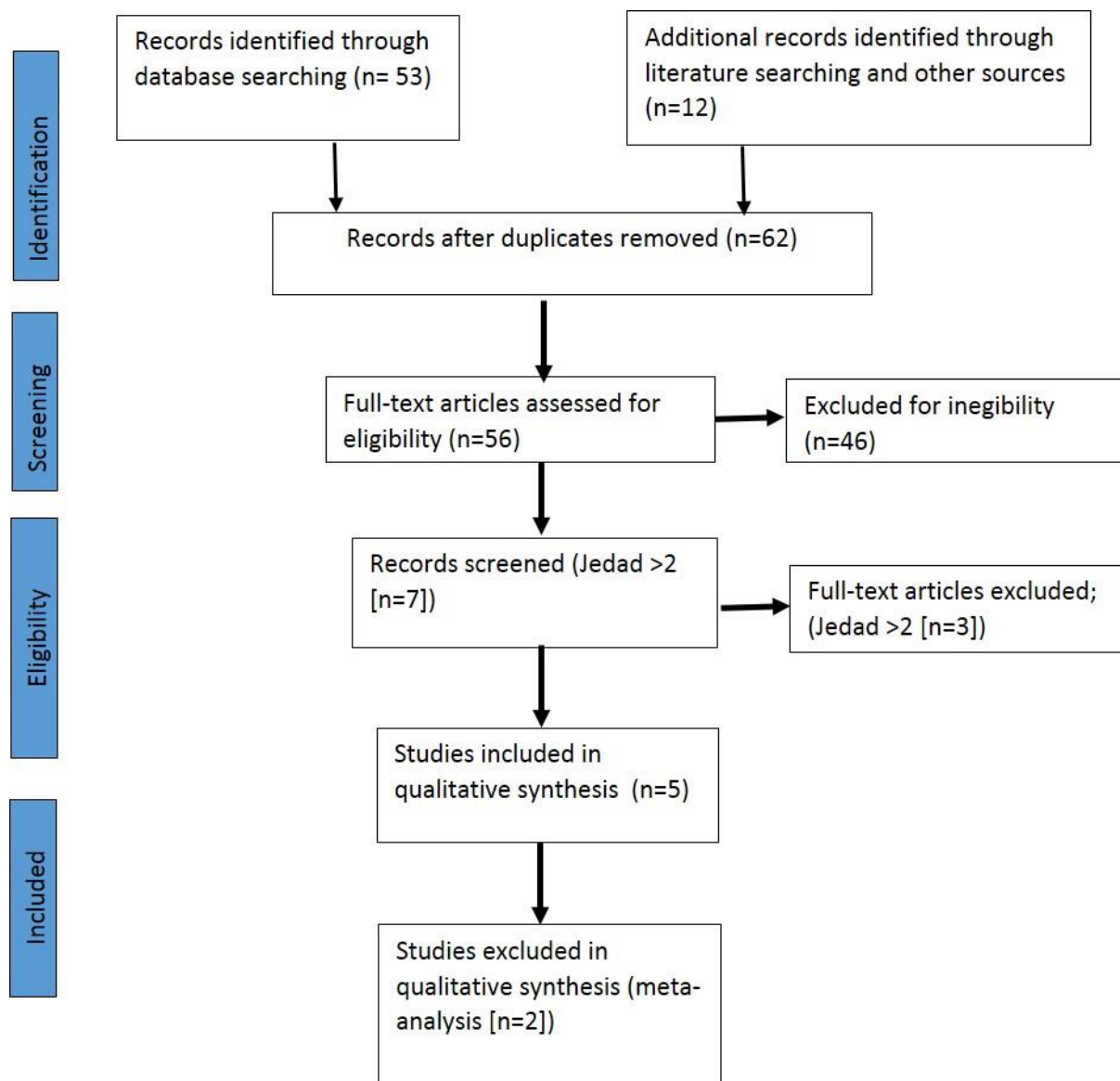


Figure 1. Systematic literature review process. The flow diagram describes the systematic review of the literature for the mortality by COVID-19 in patients with diabetes.

The studies general characteristics such as authors' names, studies' objectives, place of recruitment, study type and conclusion are shown in table 1.

Table 1. General characteristics of studies considered for the outcome mortality in patients with diabetes.

Authors	Objectives	Place/type	Conclusion
Fei Zhou et al 2020	to explore risk factors of in-hospital death for patients and describe the clinical course of symptoms, viral shedding, and temporal changes of laboratory findings during hospitalization.	Jinyintan Hospital/ retrospective, multicentre cohort study	older age, higher SOFA score, and elevated d-dimer at admission were risk factors for death of adult patients with COVID-19. The prolonged viral shedding provides the rationale for testing novel coronavirus antiviral interventions in efforts to improve outcomes.
Chaomin Wu et al 2020	To describe the clinical characteristics and outcomes in patients with COVID-19 pneumonia who developed acute respiratory distress syndrome (ARDS) or died.	Zhongshan Hospital/ Retrospective cohort study	Older age was associated with greater risk of developing ARDS and death, probably because of less rigorous immune response. Although fever was associated with the development of ARDS, it was also associated with better outcomes. Several factors related to the development of ARDS were not associated with death, which indicates that different pathophysiological changes from hospital admission to development of ARDS and from development of ARDS to death may exist. Moreover, treatment with methylprednisolone may be beneficial for patients who develop ARDS. Double-blinded randomized clinical trials to determine the most effective treatments for COVID-19 are still needed.
Mingli Yuan et al 2020	To summarize the clinical and radiologic characteristics of 27 confirmed cases and analyze the association of radiologic findings with mortality cases	University of Science and Technology, Wuhan, Hubei, China /retrospective	A simple CT scoring method was capable to predict mortality
Xiaobo Yang et al 2020	We aimed to describe the clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia	Wuhan, China/ retrospective, observational study	the mortality of critically ill patients with SARS-CoV-2 pneumonia is high. The survival term of the non-survivors is likely to be within 1–2 weeks after ICU admission. Older patients (>65 years) with comorbidities and ARDS are at increased risk of death. The severity of SARS-CoV-2 pneumonia poses great strain on hospital critical care resources, especially if they are not adequately staffed or resourced.
W. Guan et al 2020	describe the results of our analysis of the clinical characteristics of Covid-19 in a selected cohort of patients throughout China	Hospital of Guangzhou Medical University/ retrospective	During the first 2 months of the current outbreak, Covid-19 spread rapidly throughout China and caused varying degrees of illness. Patients often presented without fever, and many did not have abnormal radiologic findings. (Funded by the National Health Commission of China and others

Table 2 shows COVID-19 mortality for patients with and without diabetes according to each study. The lowest mortality rate in patients with and without diabetes was found by W. Guan et. al.

2020 (22.3 and 6.4%, respectively). No other author found similar mortality rate among groups; for all, the mortality rate in patients with diabetes was higher compared to non-diabetic patients. The HB1Ac level and time of diagnosis of diabetes was reported only by a study.

Table 2. General characteristics of studies as to overall mortality and diabetes mortality rates.

Studies	Sample size, (n)	Overall mortality rate (except diabetics), n(%)	Diabetic patients, n (%)	Alive, n(%)	Death, n(%)
Fei Zhou et. al., 2020 ¹⁷	191	36(18.8)	36(19)	19(52.7)	17(47.3)
Chaomin Wu et. al., 2020 ²	84	33(39.2)	16(19.1)	5(31.7)	11(68.8)
Mingli Yuan et. al., 2020 ²⁵	27	4(14.8)	6 (22.2)	0(0)	6(100)
Xiaobo Yang et. al., 2020 ²²	52	25(48.1)	9 (17.3)	2(12.3)	7(77.7)
W. Guan et. al., 2020 ⁴	1099	71(6.4)	81(7.3)	63(77.7)	18(22.3)

Death risk among diabetic patients was compared to individuals without diabetes in each of the studies. In Fei Zhou et. al. study, the risk was 3.9 (CI 95% of 2.1 to 7.9, $p < 0.0001$); for Chaomin Wu et. al., it was 3.3 (CI 95% of 1.8 to 5.9, $p < 0.0001$); In Mingli Yuan et. al., 5.9 (CI 95% from 4.5. to 29, $p < 0.0001$); in Xiaobo Yang et. al., 6.4 (CI 95% from 3.1 to 13.4, $p < 0.0001$); and, finally, in W. Guan et. al., 3.7 (CI 95% from 1.5 to 8.0, $p < 0.002$) (Figure 2).

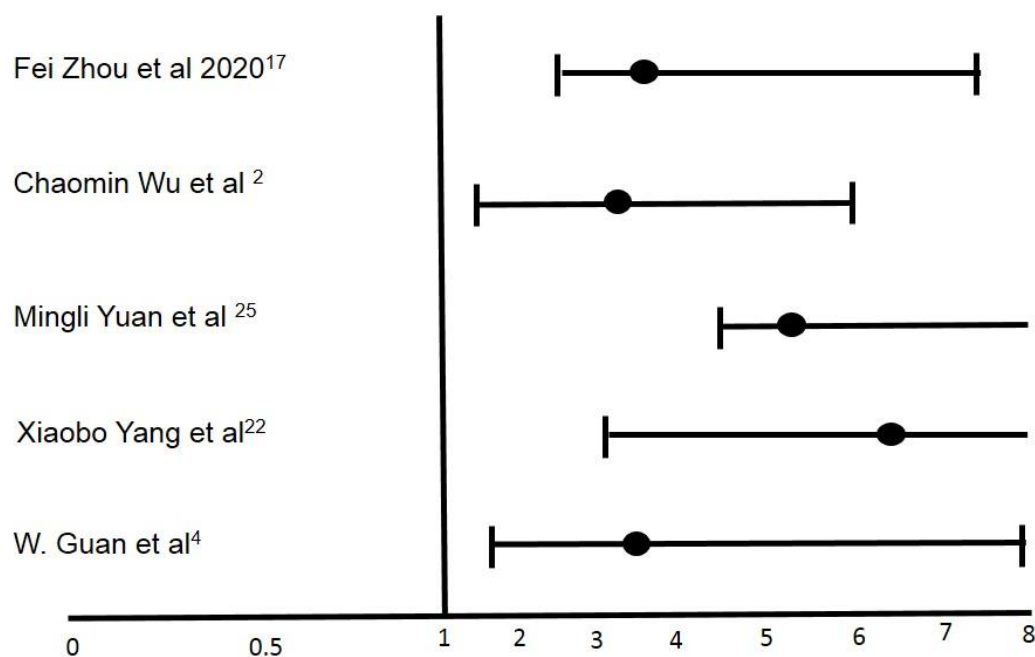


Figure 2. Forest plot of studies investigating mortality risk in patients with diabetes mellitus

Based on the final studies analysis, a global average mortality risk of COVID- 19 in patients with diabetes was assessed. It was seen that the mortality risk was 8.9 times higher for patients with diabetes than individuals without it (Figure 3).

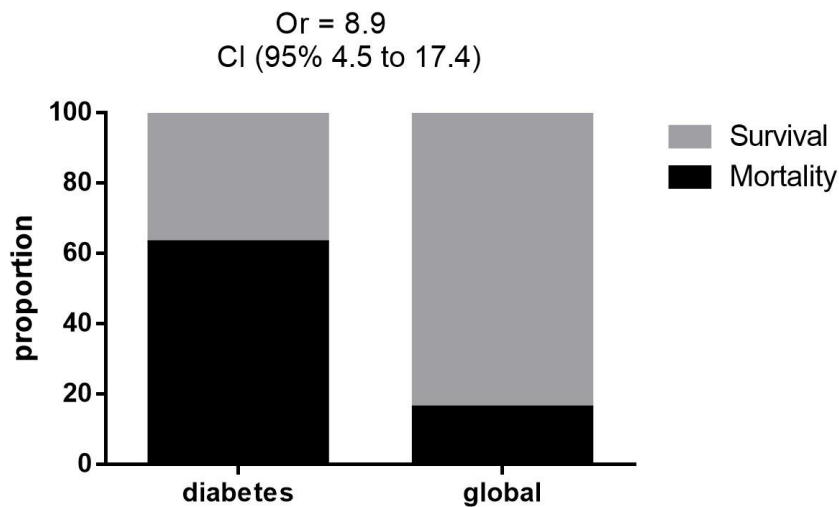


Figure 3 - Global mortality risk of COVID-19 in patients with diabetes

4. Discussion

The aim of this systematic review was to identify COVID- 19 mortality rate and risk among patients with diabetes. Our review showed that mortality rate due to COVID- 19 varied widely according to each study, however, all the mortality rates were higher among patients with diabetes. Nevertheless, while evaluating the average mortality risk for patients with diabetes in relation to non-diabetic patients, OR was 8.9 times higher. The new finding is that the Hb1Ac level and diagnosis time can contribute to higher mortality.

In one of the first published studies evaluating the mortality risk of COVID- 19, the authors showed that older age, high SOFA score and d-dimer greater than 1 µg / mL could help clinicians to identify patients with poor prognosis at an early stage¹⁷. Also, it is known that the age-dependent defects in T-cell and B-cell functioning and the excess production of type 2 cytokines could lead to a deficiency in viral control replication and more prolonged proinflammatory responses, potentially leading to poor outcome¹⁸. It is known that the sofa severity scale is also a good marker of mortality in patients with sepsis¹⁹; it has been shown that sepsis occurs in about 40% of patients with COVID- 19 due to pneumonia²⁰.

After these findings, other studies began to evaluate other prognostic factors, such as heart disease, arterial hypertension, chronic obstructive lung disease, chronic kidney disease and carcinoma²¹⁻²³. Diabetes and uncontrolled glycaemia were reported as significant predictors of

severity and deaths in patients infected with different viruses - including the 2009 pandemic influenza A (H1N1)²⁴, SARS-CoV²⁵ and MERS-CoV²⁶. Previous studies have shown the risk of complications of COVID-19 in patients with diabetes, with increased rates in ICU admission and mechanical ventilation need^{7,9}.

Most recently, a meta-analysis showed that diabetic patients with COVID-19 infection have a higher risk of ICU admission and higher mortality risk²⁷. A relationship between diabetes and infection has long been clinically recognized²⁸. Infections - particularly influenza and pneumonia - are common and more serious in older people with type 2 diabetes mellitus²⁸. However, there is no evidence whether diabetes itself increases susceptibility of infections developing in these patients. Still, it remains uncertain how exactly the inflammatory and immune response occurs in patients COVID-19, as well as whether hyper or hypoglycemia may alter the SARS-CoV-2 virulence or the virus itself interferes with insulin secretion or glycaemic control.

There are several hypotheses for which the patient with diabetes has complications due to COVID-19. Chronic inflammation, increased coagulation activity, immune response impairment and potential direct pancreatic damage by SARS-CoV-2 might be among the underlying pathophysiological mechanisms contributing to the increased morbidity and mortality of COVID-19 in people with diabetes²⁹.

Another possibility is that diabetes is a chronic inflammatory condition characterized by multiple metabolic and vascular abnormalities that can affect its response to pathogens³⁰. Hyperglycemia and insulin resistance promote increased synthesis of glycosylation end products (AGEs) and oxidative stress, and proinflammatory cytokines; in addition, it stimulates the production of adhesion molecules that mediate tissue inflammation^{14,15}. This inflammatory process may be part of the underlying mechanism that leads to a greater propensity to infections - worse results in patients with diabetes³¹.

Insulin resistance and T2DM are associated with endothelial dysfunction and increased platelet aggregation and activation. These abnormalities predispose the hypercoagulable prothrombotic state development³². It is possible that coagulation disorders are one of the main mechanisms that increase mortality of COVID-19 among patients with diabetes. Coronavirus inoculation has already been found in pancreatic islets. Therefore, although more evidence is needed, pancreatic damage may also be present in patients with COVID-19, possibly contributing to a higher risk of mortality in diabetic patients³³.

Although diabetes is associated with worse prognosis for COVID-19 patients, the susceptibility to COVID-19 infection does not appear to be greater than non-diabetic individuals. According to several studies, the prevalence of diabetes in people infected with the virus is about the same as the overall population, even slightly lower³⁴⁻³⁵.

The limitations of this study are related to the fact that we did not carry out risk analysis corrected by age and sex; as it is already known that age, as well as, male gender can influence higher mortality rates. Nevertheless, this study has important clinical applications related to the fact that the increase in mortality in diabetic patients may be related to coagulation disorders and pancreatic changes.

5. Conclusion

According to the presented analyzes, we can conclude that mortality risk and mortality observed in COVID-19 disease is higher among patients with diabetes than individuals without it. This can be partially explained by changes in its disease mechanism, such as blood clotting and abnormal pancreas functioning.

6. Reference

1. AL Phelan, R Katz, LO Gostin The novel coronavirus originating in Wuhan, China: challenges for global health governance JAMA (2020). published online Jan 30. DOI:10.1001/jama.2020.1097
2. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. Published online March 13, 2020. doi:10.1001/jamainternmed.2020.0994.
3. Universidade John Hopkins, autoridades locais Última atualização em 19 de abril de 2020 06:00 GMT. <https://www.bbc.com/portuguese/internacional-51718755> visitado em 19 de abril de 2020
4. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... & Guan, L. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*.
5. Baud, D., Qi, X., Nielsen-Saines, K., Musso, D., Pomar, L., & Favre, G. (2020). Real estimates of mortality following COVID-19 infection. *The Lancet infectious diseases*.
6. COVID, C., & Team, R. (2020). Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–March 16, 2020. *MMWR Morb Mortal Wkly Rep*, 69(12), 343-346.
7. Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., ... & Li, X. (2020). A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine*.
8. Badawi, A. & Ryoo, S. G. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *Int. J. Infect. Dis.* 49, 129–133 (2016).

9. Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395, 497–506 (2020).
10. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, Bi Z, Zhao Y. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol.* 2020. doi: 10.1007/s00392-020-01626- [Epub ahead of print]
11. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; published online Feb 7. DOI:10.1001/jama.2020.1585.
12. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. *Diabetes Care.* 41 (2018) 2127-2135.
13. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* S2213-2600(20)30116-8 (2020). doi: 10.1016/S2213- 2600(20)30116-8. [Epub ahead of print]
14. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020. doi: 10.1111/all.14238. [ahead of print]
15. Wu Z, McGoogan JM. 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. doi: 10.1001/jama.2020.2648 [Epub ahead of print]
16. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
17. Fei Zhou*, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study
18. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. *Clin Infect Dis* 2005; 41 (suppl 7): S504–12.
19. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001; 286: 1754–58.
20. Zhou F, Wang Y, Liu Y, et al. Disease severity and clinical outcomes of community-acquired pneumonia caused by non-influenza respiratory viruses in adults: a multicentre prospective registry study from the CAP-China Network. *Eur Respir J* 2019; 54: 1802406.
21. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia Wuhan, China: a descriptive study. *Lancet* 2020; 395: 507–13.

22. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; published online Feb 24. [https://doi.org/ 10.1016/S2213-2600\(20\)30079-5](https://doi.org/10.1016/S2213-2600(20)30079-5).
23. National Health Commission of the People's Republic of China. Chinese management guideline for COVID-19 (version 6.0). Feb 19, 2020. <http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2/files/b218cfef1bc54639af227f922bf6b817.pdf> (accessed Feb 19, 2020; in Chinese).
24. Schoen K, Horvat N, Guerreiro NFC, de Castro I, de Giassi KS. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. *BMC Infect Dis*. 2019;19(1):964. Epub 2019/11/14. doi: 10.1186/s12879-019-4592-0. PubMed PMID: 31718571; PubMed Central PMCID: PMC6852716.
25. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med*. 2006;23(6):623-8. Epub 2006/06/09. doi: 10.1111/j.1464-5491.2006.01861.x. PubMed PMID: 16759303.
26. Banik GR, Alqahtani AS, Booy R, Rashid H. Risk factors for severity and mortality in patients with MERS-CoV: Analysis of publicly available data from Saudi Arabia. *Virol Sin*. 2016;31(1):81-4. Epub 2016/01/31. doi: 10.1007/s12250-015-3679-z. PubMed PMID: 26826080
27. Roncon L, Zuin M, Rigatelli G, Zuliani G, Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome, *Journal of Clinical Virology* (2020), doi: <https://doi.org/10.1016/j.jcv.2020.104354>
28. Pearson-Stuttard J, Blundell S, Harris T, Cook DG, Critchley J. Diabetes and infection: assessing the association with glycaemic control in population-based studies. *Lancet Diabetes Endocrinol*. 2016;4(2):148-58. Epub 2015/12/15. doi: 10.1016/S2213-8587(15)00379-4. PubMed PMID: 26656292.
29. Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besançon S, et al. Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2020 Feb 13:108072. doi: 10.1016/j.diabres.2020.108072.
30. Knapp S. Diabetes and infection: is there a link?--A mini-review. *Gerontology*. 2013;59(2):99-104. Epub 2012/11/28. doi: 10.1159/000345107. PubMed PMID: 23182884.
31. Petrie JR, Guzik TJ, Touyz RM. Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. *Can J Cardiol*. 2018;34(5):575-84. Epub 2018/02/21. doi: 10.1016/j.cjca.2017.12.005. PubMed PMID: 29459239; PubMed Central PMCID: PMC68593551.
32. Dunn EJ, Grant PJ. Type 2 diabetes: an atherothrombotic syndrome. *Curr Mol Med*. 2005;5(3):323-32. Epub 2005/05/17. doi: 10.2174/1566524053766059. PubMed PMID: 15892651.
33. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol*. 2010;47(3):193-9. Epub 2009/04/01. doi: 10.1007/s00592-009-0109-4. PubMed PMID: 19333547; PubMed Central PMCID: PMC68593551.

34. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol.* 2020. Epub 2020/03/13. doi: 10.1007/s00392-020-01626-9. PubMed PMID: 32161990.
35. Porto EF, Domingues AL, Souza AC, Miranda MKV, Froes MBC, Pasqualinoto SRV. Mortality due to Covid-19 in Brazil: sociodemographic profile of the first weeks. *Research, Society and Development*, 2021;10(1): e34210111588.