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### Clinical evolution of COVID-19 patients with hypertension and/or diabetes in the intensive care units: a systematic review

### Evolução clínica de pacientes com COVID-19 e hipertensos e/ou diabéticos nas UTI: uma revisão sistemática

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#### ABSTRACT

We aimed to evaluate the association of hypertension and diabetes with the severity prognosis of COVID-19 in ICU hospitalization by analyzing significant differences in epidemiological, clinical and laboratory aspects when compared with non-diabetic and non-hypertensive patients. This review was conducted according to PRISMA, registered on PROSPERO, guided for 4 independent researchers, we used 5 different database and Newcastle-Ottawa scale was the bias analysis applied. A total of 26 articles were included in this review. Diabetics patients admitted to the ICU were older than non-diabetics, about 10 years. Males were associated with a higher chance of death compared to females. Patients with newly diagnosed diabetes and poorly controlled HBA1C had a higher risk of death compared to long-term and controlled patients. Diabetic patients presented evidence that this population tends to have more symptoms in the lower respiratory tract than upper respiratory tract. Procalcitonin levels and CRP proved to be determinant for the patient's evolution. Hypertensive and diabetics patients who died presented higher d-dimer levels, troponin and NT-proBNP on ICU admission in comparison to patients who survived. Creatinine was higher and this was a marker of severity as it was associated with death. Gender plays an important role in mortality, also advanced age. Diabetes is an independent risk factor for mortality of COVID-19 and mortality, but hypertension is not. We conclude that hypertension and diabetes were significantly associated with COVID-19 patient's admission to the ICU.

Key words: COVID-19, Diabetes, Hypertension, ICU, Prognosis.

#### RESUMO

Objetivou-se avaliar a associação da hipertensão e do diabetes com o prognóstico de gravidade da COVID-19 nas internações em UTI analisando diferenças significativas nos aspectos epidemiológicos, clínicos e laboratoriais quando comparados aos pacientes não diabéticos e não hipertensos. Esta revisão foi realizada de acordo com o PRISMA, registrado no PROSPERO, orientado por 4 pesquisadores independentes, foram utilizados 5 diferentes bancos de dados e a escala de Newcastle-Ottawa foi a análise de viés aplicada. Um total de 26 artigos foram incluídos. Pacientes diabéticos admitidos na UTI eram mais velhos do que não diabéticos, cerca de 10 anos. Os homens foram associados a uma maior chance de morte em comparação com as mulheres. Pacientes com diabetes recém-diagnosticado e HBA1C mal controlada tiveram maior risco de morte em comparação com pacientes de longo prazo e controlados. Pacientes diabéticos apresentaram evidências de que essa população tende a apresentar mais sintomas no trato respiratório inferior do que no

Falcão, S. O. et al. / Revista de Ensino, Ciência e Inovação em Saúde v. 4 n. 1 (2023) p. 27-38

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superior. Os níveis de procalcitonina e PCR mostraram-se determinantes para a evolução do paciente. Pacientes hipertensos e diabéticos que morreram apresentaram maiores níveis de d-dímero, troponina e NT-proBNP na admissão em UTI em comparação aos pacientes que sobreviveram. A creatinina foi maior e foi um marcador de gravidade por estar associado ao óbito. O gênero desempenha um papel importante na mortalidade, como também a idade avançada. O diabetes é um fator de risco independente para a mortalidade por COVID-19, mas a hipertensão não é. Conclui-se que hipertensão e diabetes foram significativamente associados à admissão do paciente COVID-19 na UTI. Palavras-chave: COVID-19, Diabetes, Hipertensão, UTI, Prognóstico.

## INTRODUCTION

Since 2019, the world has been facing a battle against a virus that, due to its rapid spread, has infected many people, taking some to ICU, collapsing all the health systems in the world and led to thousands of deaths.<sup>1</sup> COVID-19 has become one of the most studied subjects recently, however, there are still gaps to be filled, especially in regard to why this virus affects people differently, so that a possible patient prognosis can be predicted.

Current studies show a wealth of information on mortality rates, comorbidity and other risk factors associated with the severity of the infection. The severe condition can occur in any individual, even in those without any comorbidity, however, there is a higher prevalence of severity among those with chronic diseases, such as cardiovascular diseases, hypertension, diabetes, cancer, lung diseases, among others.<sup>1-3</sup>

We also know that patients with chronic comorbidities often end up being vulnerable to severe progression when they are victims of infectious processes. Among these comorbidities, hypertension and diabetes stand out among those infected with SARS-CoV-2 due to their high prevalence among patients admitted to the ICU for Covid-19 and, in addition, hypertensive and diabetic patients are groups at higher risk, severity, including ICU admission, use of invasive mechanical ventilation, and death.<sup>4,5</sup>

The severity of Covid-19 in this population is related to several changes in the body of patients with these two chronic diseases, such as endothelial damage, exacerbated inflammatory response, secondary damage to target organs, deficiency in the action of the immune system, among other damages that make it difficult to adequate fight against Sars-Cov-2 infection compared to healthy individuals.<sup>6,7</sup>

With this in mind, it is necessary to elucidate the clinical evolution of patients with hypertension and/or diabetes admitted to the ICU with Covid-19 through the analysis of epidemiological, clinical and laboratory

information, establishing correlations between these data and the outcome of these patients.

Thus, the authors of this study have as their initial, observing a demand for studies about COVID at uti, especially with patients with such prevalent comorbidities objective to carry out a systematic review to analyze studies carried out with hypertensive and diabetic patients admitted to the ICU to obtain prognostic conclusions about this population and subsequently a meta-analysis of association can be performed.

## MATERIAL AND METHODS

The search was carried out in 5 different databases by 4 independent researchers: Web of Science, PUBMED, Science Direct, LILACS and SciELO, during the 2nd semester of 2021. We followed the PRISMA guidelines and registered on PROPERO (ID: CRD42021282066).<sup>8</sup>

The descriptors were: 'diabetes', 'ICU', 'hypertension' and 'covid-19', including MESH terms. These descriptors were combined with AND and OR operators, depending on the database.

The search engines were: PubMed: ((covid-19[mesh terms]) and (diabetes[mesh terms])) and (ICU[mesh terms]) or ((covid-19[mesh terms]) and (hypertension[mesh terms])) and (ICU[mesh terms]), Science Direct: (covid-19 and hypertension and ICU) or (covid-19 and diabetes and ICU), Web of Science: (covid-19 (topic) and (diabetes or hypertension) (title) and ICU (topic)), LILACS: (covid-19 and (diabetes or hypertension) and ICU) and SciELO: (covid-19 and (diabetes or hypertension) and ICU).

The inclusion criteria were as a restriction tool, we used the English language, the publication period from 01-01-2020 to 07-08-2021 and only original articles were included. The exclusion criteria were: children or pregnant women samples, studies about medicine efficacy, other comorbidities, systematic reviews, meta-analysis and service experience report.

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In addition, we applied filters to each database, as follows: PubMed (Full text, Bibliography, Books and Documents, Case Reports, Classical Article, Clinical Conference, Clinical Study, Clinical Trial, Clinical Trial Protocol, Comparative Study, Congress, Consensus Development Conference, Controlled Clinical Trial, Dataset, Evaluation Study, Government Publication, Guideline, Historical Article, Introductory Journal Article, Journal Article, Letter, Multicenter Study, Newspaper Article, Observational Study, Periodical Index, Practice Guideline, Pragmatic Clinical Trial, Randomized Controlled Trial, Technical Report, Twin Study, Validation Study, Humans), Science Direct (2020, 2021, research articles and case reports), Web of Science (Document Types: Articles or Letters), LILACS (english) and SciELO (english).

After selecting the articles, all duplicates were discarded. Then, the researchers carried out the next exclusion using the title of the publication as a criterion, articles without the descriptors

'diabetes' or 'hypertension' in the title were excluded. Then, four independent researchers carefully read the abstracts and those articles in which at least three researchers opted for inclusion were chosen. In case of disagreement between the examiners, a fifth researcher was consulted to decide whether or not to include the article.

Articles that met the inclusion criteria were subjected to bias analysis using the NewCastle-Ottawa scale.<sup>9</sup> Those with low to moderate risk (8-6) were included and those with severe bias (>6) were excluded.

Finally, the articles were divided among four researchers through a raffle and were read in full, analyzed and the epidemiological data (gender, age, comorbidities, etc.) laboratory (blood count, creatinine, urea, lactate dehydrogenase (LDH) and VHS (velocity of hemosedimentation), C reactive protein (CRP), etc.) and radiological data collected and entered into an Excel table. However, radiological information was discarded due to insufficient data.

## RESULTS

The search resulted in a total of 292 articles. Eliminating the duplicates, 250 articles remained. We applied the inclusion and exclusion criteria by the articles' titles, eliminating 167 articles and keeping 87 articles to the next step. Then, we carefully read the abstracts and excluded 54 articles. The remaining 30 articles were submitted to the bias analysis for the Newcastle-Ottawa Scale.<sup>9</sup> Of these, 4 were eliminated due to severe risk of bias and, finally, 26 articles remained to be analyzed in detail in this systematic review, there is supplementary material with the application of bias and most important results of all.

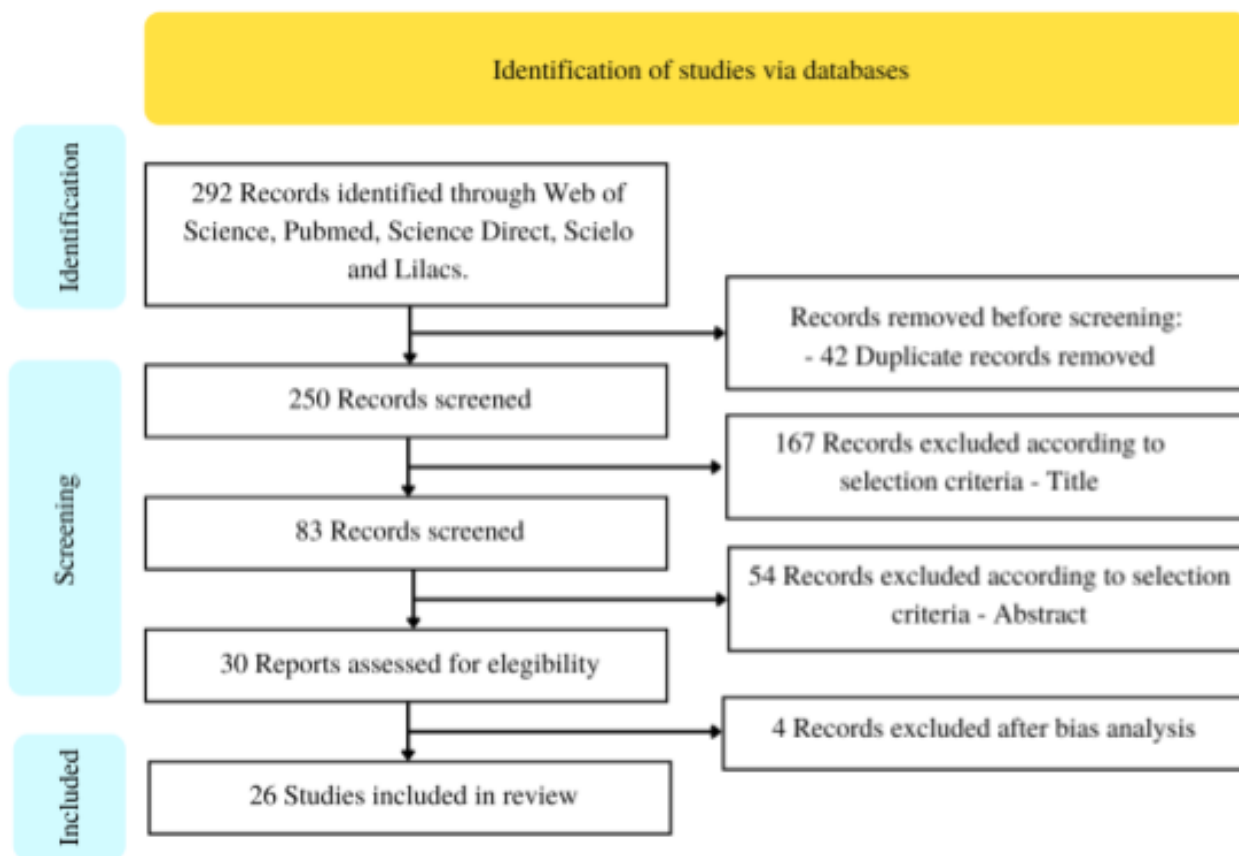
The results of this review are classified in a qualitative way in order to organize the data as epidemiological, clinical and laboratorial data and reveal the impact on the patient's prognosis, especially in patients with hypertension and diabetes admitted to the ICU, there is supplementary material to know better our sample, with total of cases, sex and median age.

### *Epidemiological findings*

The studies found in this systematic review brought some important epidemiological data about the samples that were analyzed. Relevant information about diabetic patients includes findings on age, sex, duration of illness, comorbidities, mortality, and previous medication use. However, in the hypertension articles, we found data about age, mortality and previous medication use.

We found that diabetics patients admitted to the ICU were older than non-diabetics, about 10 years<sup>10-13</sup> and, comparing survivors with non-survivors, the first group was substantially younger.<sup>14,15</sup> In parallel, two articles showed that there was no relationship between age and unfavorable prognosis.<sup>16,17</sup> Among hypertensive individuals, there was a significant association between advanced age and death.<sup>18,19</sup> Furthermore, studies carried out in the United Arab Emirates<sup>11</sup>, Turkey<sup>14</sup> and Greece<sup>17</sup> showed that male patients with DM compose the majority of those admitted to the ICU, with rates above 66%, however, a study carried out in China

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**Figure 1. Diagram of the research process and articles selection.**

revealed that the female patients were dominant in Covid-ICU (85.7%).<sup>20</sup> In addition, a Turkish study revealed that males were associated with a higher chance of death compared to females (OR 1.09, 95% CI, 1.05 – 1.13).<sup>14</sup>

In Wuhan<sup>16</sup>, patients with diabetes for a longer time had a worse prognosis. While in Hunan province<sup>20</sup>, the average duration of DM was not related to a higher chance of death.<sup>20</sup> Moreover, others Chinese researchers<sup>21</sup> demonstrated that patients with newly diagnosed diabetes had a higher risk of death compared to long-term patients, regardless of whether they had a higher cardiovascular risk (RR 3.06 vs 1.55;  $p = 0.004$ ) and this finding was corroborated by Italians (HR 9.42; 95% CI 2.18-40.7).<sup>13</sup>

It is unanimous among studies that diabetics who evolved with more severe Covid-19 had a higher proportion of comorbidities, especially those associated with heart disease, such as hypertension, coronary artery disease and ischemic heart disease.<sup>10, 11, 14, 15, 22-26</sup> Less frequently, additional comorbidities were present in these patients, such as: chronic kidney disease,

chronic obstructive pulmonary disease, asthma, dyslipidemia, heart failure, and cerebrovascular diseases.<sup>13, 14, 22, 24-26</sup> However, the most common comorbidity among them was hypertension<sup>11, 17, 23, 24, 26, 27</sup>, which is associated with a death increase due to the disease, according to data collected from Tongji Hospital in Wuhan (57 vs 16  $p < 0.001$ ).<sup>23</sup>

Obese patients were more likely to die (OR 2.36, 95% CI, 1.18-4.74).<sup>14, 27</sup> In fact, the presence of obesity increased the risk of death by 3.17 times and the risk of severe forms of Covid-19 was 1.25 times greater in obese patients, requiring a prolonged invasive mechanical ventilation compared to those without obesity ( $12.63 \pm 7.2$  vs.  $11.57 \pm 6.7$  days  $p = 0.384$ ).<sup>27</sup>

We found different outcomes regarding the mortality data: three articles reported that the survival chances are similar between diabetics and non-diabetics<sup>20, 28, 29</sup> and two of them reported greater chance of complications.<sup>20, 28</sup> Some studies demonstrated the presence of diabetes was associated with a greater chance of death, with a risk ranging from 1.38 to 8.76 times greater than in non-diabetics.<sup>12, 14, 21, 24, 27</sup> On the other hand,



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Chicago's hospital showed the mortality of non-diabetics was higher than diabetics, however, diabetics were more likely to be intubated (OR 3.00; 95% CI, 1.39 to 6.46).<sup>26</sup>

Additionally, hypertensive individuals presented a higher risk of death than normotensive individuals.<sup>19</sup>

Lastly, only two articles on diabetes brought the use of previous medications and their relationship with the prognosis of patients. One of them reported that those who were using statins, acetylsalicylic acid, angiotensin-converting enzyme blockers and insulin presented a higher risk of death, once these patients present multiple comorbidities.<sup>14</sup> The other one showed that diabetics treated with metformin or sulfonylureas present a lower death rate compared to those who were on a treatment regimen with other drugs.<sup>29</sup>

Regarding hypertensive patients, those who used angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were less likely to be admitted to the ICU (HR: 0.21, 95% CI: 0.06–0.73)<sup>30</sup> and there was no greater chance of death in this group compared to those who were using other antihypertensives (22.9% (n=8) vs. 43.1% (n=25),  $p = 0.048$ ).<sup>18</sup> Farther, those who were not using Angiotensin Receptor Blocker (ARBs) were more likely to have heart failure (HR = 1.73, 95% CI: 1.19–2.51) than patients who were using this class of antihypertensive drug.<sup>30</sup>

### *Clinical findings*

Fever was the most common sign in diabetic patients.<sup>16, 20, 31</sup> 65,9% of those presented with fever with a temperature ranging from 37,3°C to 39°C.<sup>16</sup> Cough was also a common symptom, followed by shortness of breath.<sup>16, 20, 31</sup> On hypertensive patients, cough was the most common (45%), followed by fatigue (21.5%), chest tightness and shortness of breath (16.8%).<sup>28</sup>

The rate of severe COVID-19 in patients with diabetes mellitus (DM) is higher than non-DM patients, as well as higher percentage of ICU admission, intubation and death.<sup>11, 22, 31</sup> Diabetics had a higher prevalence of serious complications when compared to non-diabetics, such as sepsis, heart failure and kidney injury ( $p < 0.001$ ).<sup>11</sup>

Studies about diabetic patients presented evidence that this population tends to have more symptoms in the lower respiratory tract than upper respiratory tract compared to non-diabetics patients affected by COVID-19.<sup>10, 20, 31</sup> This is evidenced due to increased sputum production<sup>16,31</sup>, less rhinorrhea<sup>20</sup>, shortness of breath<sup>20</sup>, and lower

oxygen saturation.<sup>16, 31</sup> The respiratory rate was significantly higher in ICU diabetics patients compared with non-ICU diabetics patients.<sup>10</sup> It may be the cause of longer illness duration in diabetics.<sup>16, 31</sup> Diabetic patients who evolved to the severe form, had more symptoms at hospital admission, including fever, cough, dyspnea and fatigue compared with those not admitted in ICU<sup>31</sup> or the non-diabetics in ICU.<sup>11, 20, 22, 23</sup>

Cardiovascular parameters such as pulse pressure, systolic blood pressure (SBP) and unstable systolic/diastolic blood pressure ratio control were independently associated with greater risks of adverse outcomes, including mortality.<sup>14, 28</sup> Mortality rates in hypertensive patients is 16,8% versus 6,8% in patients without hypertension.<sup>30</sup> Patients who present higher SBP and/or DBP elevations on hospital admission were more likely to progress to a severe form of the disease, raising the need for ICU admission, invasive mechanical ventilation use and acute respiratory failure.<sup>21</sup> However, hypertensive patients with controlled and stable blood pressure below 130/80 mmHg were most likely to have a favorable prognosis.<sup>14, 21</sup>

Comparative analysis between patients with and without hypertension affected by COVID-19 showed over 45 years of age prevalence among hypertensive patients.<sup>19</sup> Besides, diabetes, coronary diseases, obesity and smoking are more frequent in hypertensive patients than patients without hypertension.<sup>29</sup> In-hospital outcomes, like ICU stay and receiving mechanical ventilation, were mostly presented in patients with hypertension ( $p < 0.001$ ).<sup>29</sup>

### *Laboratorial findings*

Through laboratorial analysis, it is possible to verify alteration in blood elements, immunological and biochemical markers, aside from cardiac, renal and hepatic biomarkers.

Blood elements are altered during the COVID-19 infection. The lymphopenia in diabetics was associated with severity, mortality and longer hospitalization time.<sup>12, 14, 20, 23, 28</sup> The leukocytosis was associated with greater need for hospitalization in ICU<sup>28, 31</sup>, maybe because the neutrophilia ( $7.25 \times 10^9/L$ )<sup>11, 23, 26, 31</sup> accompanied by the increased levels of IL-6, indicates a marked inflammatory response in this group.<sup>18, 23, 31</sup> The increased levels of IL-6 (about 7xs) was associated with greater need for hospitalization in ICU<sup>31</sup> and worse prognosis<sup>18</sup>, with higher mortality in diabetics and hypertensive patients.<sup>23</sup> Lactate dehydrogenase (LDH) and VHS (velocity of hemo

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sedimentation) were higher in diabetics admitted to the ICU compared to those not in intensive care (465U/L vs 330 U/L)<sup>23, 31</sup>, and even higher on patients who evolved to death.<sup>17, 21, 29</sup>

Other inflammatory markers presented increased levels when the patients were hospitalized, as C reactive protein (CRP)<sup>10, 12, 14, 16, 18, 21, 23, 29, 31</sup> and procalcitonin<sup>18, 22, 23, 31</sup> because of hyperglycemia, with glucose levels >11 mmol/L<sup>16, 29</sup>. The increased CRP levels raise the chance of ICU needing among diabetics, especially when CRP>15 mg/L<sup>10, 31</sup> and CRP was even higher (mean of 97.2 mg/L) in patients who died, which indicates that the non-survivors diabetics had a more severe inflammatory response.<sup>23</sup> Procalcitonin levels proved to be determinant for the patient's evolution.<sup>22, 23, 31</sup> The non-survivor diabetics presented higher levels of procalcitonin in comparison to the survivors and those with mild COVID (20.5 vs 0.53ng/mL).<sup>22, 23</sup> Hypertensive patients who died present higher CRP levels (106.4mg/L) and procalcitonin (0.12 ng/mL), on admission, in relation to the survivors (40.7 mg/L CRP and 0.05 ng/mL procalcitonin).<sup>18</sup>

The precedent diabetic marker, HBA1C levels, were controversial on ICU admission: in a Hunan population, the HBA1C was increased (7.5 - 9.5) in diabetic ICU patients, compared to diabetics patients not in ICU (6.2 - 7.5)<sup>20</sup> and in Wuhan there was no difference between levels of ICU and non-ICU patients.<sup>31</sup> Those with poorly controlled HBA1C - especially greater than 8.6% - present an increased risk of worsening.<sup>29, 32</sup> At the same time, the random blood glucose concentrations were higher in ICU diabetic patients.<sup>31</sup> The cardiac biomarkers were altered in patients who evolved to death. Increased levels of D-dimer<sup>18, 20, 23, 26, 31</sup>, CK<sup>18, 22, 31</sup> and troponin<sup>13, 18, 23, 31, 33</sup> were reported among patients with diabetes or hypertension who were admitted to the ICU or died, compared with those who didn't go to ICU or die. Hypertensive and diabetics patients who died presented higher d-dimer levels (1.96 ug/ml) on ICU admission in comparison to patients who survived (0.94 ug/ml).<sup>18, 23, 33</sup> Among hypertensive patients, the highest troponin levels on admission, was indicative of poor prognosis.<sup>18, 33</sup> Lastly, N-terminal prohormone of the cerebral natriuretic peptide (NT-proBNP) increased was a factor of poor prognosis among those diabetic ICU patients who did not survive.<sup>22, 23, 31</sup> Among hypertensive individuals, NT-proBNP levels were not significant for the prognosis.<sup>18, 33</sup>

There were renal markers alterations in diabetics and hypertensive patients admitted to the ICU. In diabetics, creatinine was higher and this was a marker of severity as it was associated with death<sup>11, 26, 31</sup>, urea was high in those with severe conditions<sup>11, 12, 21</sup> and the glomerular filtration rate was smaller regardless of severity.<sup>12, 14</sup> In addition, the hydroelectrolytic disturbance observed in this group were hyperkalemia and hyponatremia compared to non-diabetics.<sup>11, 22, 28</sup> In hypertensive patients, creatinine was higher since admission, which may be related to poor blood pressure control.<sup>30</sup>

There was no evidence of liver damage, because transaminases (aspartate aminotransferase and alanine aminotransferase) were at normal levels on ICU admission.<sup>10, 23, 28, 31</sup> On the other hand, there was an indicative of liver function damage because albumin was lower in diabetics who were in the ICU and significantly low levels were found in those who died (38.30 µg/L vs 35.49 µg/L).<sup>12, 23, 31</sup> In addition, ferritin was increased in this same group of patients, comparative to normoglycemic patients (1373.0 µg/L vs 630.5 µg/L).<sup>11, 23, 29</sup>

## DISCUSSION

Hypertension was the main comorbidity found in ICU COVID-19 patients, followed by diabetes, and the association of these two diseases makes patients more vulnerable, as reported by the studies presented in this review and by a cohort carried out in the United Arab Emirates with 350 patients.<sup>11</sup> Besides, we found that most patients have cardiovascular comorbidities, but this does not mean that these comorbidities increase the risk of death or severity. Cardiovascular complications have been previously reported in respiratory infections with similar etiology and their condition affects the disease severity.<sup>34</sup>

Virus binding to angiotensin-converting enzyme 2 (ACE-2) increases cardiovascular events<sup>6</sup>, coagulation disorders<sup>35</sup>, acute kidney injury<sup>36</sup> and sometimes liver damage. These events were expected because this receptor is largely expressed on these cells' tissue and facilitates cardiovascular and coagulation events.<sup>18</sup> Viral infections cause imbalance between myocardial supply and demand, also increase systemic inflammation, rising risks for acute cardiac conditions, thrombosis, infection, and develop severe conditions during the infection.<sup>34</sup>

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Hypertension, per se, is associated with unfavorable outcomes, including hospitalization admission.<sup>37</sup> Thus, hypertensive patients have higher plasma concentrations of proinflammatory cytokines naturally, but the pathophysiological mechanisms are still not sufficiently clear. There are some hypotheses that correlate excessive activation of the renin-angiotensin-aldosterone system to lung injury, rising the inflammatory response and cytokine storm and, consequently, causing stronger cell damage.<sup>38</sup> Patients with high blood pressure may have worse prognosis than those without hypertension possibly due to differences in clinical characteristics, such as age and pre-existing comorbidities.<sup>28</sup> It is known that good blood pressure control (<130/80 mmHg) is related to a better prognosis, especially the systolic blood pressure.<sup>21</sup>

The damage induced by SARS-CoV-2 is multifactorial, high creatine levels mark acute kidney injury (AKI)<sup>36</sup>, and is related to direct cell injury resulting from viral entry through the ACE-2 receptor, pro-inflammatory cytokines caused by viral infection, in addition to a thrombotic and ischemic events.<sup>39</sup> Virus entry is responsible for podocytic dysfunction, leading to an acute proximal tubular lesion provoking tubular necrosis, which may promote a homeostasis dysregulation, glomerular dysfunction, fibrosis, vasoconstriction, local inflammation and can cause coagulation activation for ischemic glomeruli and fibrinoid necrosis due to renal microcirculatory dysfunction.<sup>39, 40</sup> It is believed that this pathology will present itself as a sentinel factor signaling a sequential organ failure, or a consequence of multiple organ failure.<sup>36</sup>

The hepatic distribution of ACE-2 is peculiar because it is highly expressed in the endothelial layer of small blood vessels, but not in the sinusoidal endothelium.<sup>41</sup> Decreased free serum albumin levels was reported in literature, indicating the presence of reactive oxygen species (ROS) and reactive nitrogen species (RNS).<sup>42</sup> Albumin binding to ROS and RNS and limits the destruction of other molecules and protects the organism.<sup>42</sup> Viral inflammatory processes lead to an overproduction of ROS and continue until the pathogens are destroyed<sup>43</sup> causing hypoxia. Hypoxia has been shown to be a main regulator of hepatocellular ACE-2 expression and lead to extra-pulmonary SARS-CoV-2.<sup>44</sup> Although liver failure does not seem to occur in the absence of pre-existing liver disease, the hepatic involvement in

COVID-19 may correlate with overall disease severity.<sup>44</sup> As long as AST and ALT indicate a preserved liver function at this review, it is possible that some damage occur, Nardo et al. observed microvesicular and macrovesicular steatosis in liver autopsies that could be a result of potential direct SARS-CoV-2 cytopathic effects and/or immunopathology induced by cytokine storm, as well as drug side effects.<sup>45</sup>

Myocardial injury is caused by a cytokine storm as a result of systemic inflammation mediated by pathologic T-cells. The storm is marked by elevated myocardial injury biomarkers, including NT-proBNP, cTnI, CRP and D-dimer which were significantly correlated with COVID-19 severity. Another hypothesis is the imbalance between supply and demand of the systemic infection along with hypoxia caused by respiratory infection, which may lead to acute myocardial injury.<sup>34</sup> It was observed that SARS-CoV-2 primarily affects the lymphocytes, especially the T cells.<sup>42</sup> The decreased lymphocytes count suggests that SARS-CoV-2 deplete immune cells and inhibits immune function. CRP is an inflammation biochemical indicator<sup>46</sup> and is well known as a sensitive acute-phase reactant and plays an instructive role in the acquired immune response<sup>47</sup>. When increased, it has strong association with the complement system activation<sup>43</sup> which is crucial to the COVID-19 progression.<sup>42</sup> Also, SARS-CoV-2 stimulates monocytes to release proinflammatory cytokines such as interleukin-6 (IL-6).<sup>43</sup>

Due to diabetics and hypertensive patients have an imbalanced inflammation response, they are more likely to evolve to a hypercoagulable prothrombotic state, closely related to a variety of thrombotic diseases, including myocardial infarction, cerebral infarction, pulmonary embolism, and venous thrombosis.<sup>48</sup> Including, myocardial injury among patients with COVID-19 is associated with increased mortality, regardless of acute respiratory distress syndrome (ARDS).<sup>49</sup> It is also known that thrombocytopenia is a characteristic present in COVID-19 and includes thrombocytopenia and platelet hyperactivation. Autopsy studies in patients with COVID-19 have shown the presence of arterial and venous thrombosis, mainly in small vessels, being associated with platelet hyperactivation, a fact that contributes to the inflammatory process. These hyperactivated platelets contribute to the regulation of leukocyte activity, stimulating the release of cytokines, mainly IL-1 $\beta$ , IL-7, IL-8 and hepatocyte

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growth factor, being at higher levels in patients with COVID-19 than those healthy. The binding of platelets to leukocytes facilitates transmigration to the alveoli, contributing to pulmonary edema. Furthermore, consumption of platelets in thrombus formation may explain thrombocytopenia in COVID-19-infected patients, which was associated with a higher risk of death compared to those with normal platelet levels. Furthermore, endothelial dysfunction has also been a feature found in COVID-19. This dysfunction leading to arteriopathy and thrombosis directly contributes to the pathophysiology of thrombotic complications associated with COVID-19, including myocardial infarction and stroke.<sup>50</sup>

Furthermore, the long-term diabetics have unfavorable outcomes and some factors justify this fact: diabetics have a deficient immune response, with low levels of C3 and C4, affecting the body's ability to fight and eliminate viruses<sup>7</sup>; there is also a reduction in the leukocytes and macrophages activity<sup>51</sup> together with an impaired innate and adaptive immune response, characterized by a state of chronic low-grade inflammation leading to multiple macrovascular and microvascular abnormalities<sup>48</sup> which promote the synthesis of numerous proinflammatory cytokines and adhesion molecules<sup>48</sup> contributing to the process of atherosclerosis and, consequently, the thrombus formation.<sup>52</sup> Because of this, diabetics with a longer diagnosis time are more likely to develop coagulopathies and have a worse clinical outcome than those who were newly diagnosed.

On the other hand, this systematic review brought some studies that indicated that newly diagnosed diabetics have a higher risk of death. One explanation for this finding is that some individuals are not aware of their diagnosis and, consequently, do not perform the appropriate treatment and suffer from the damage that a state of chronic hyperglycemia causes in various organs.<sup>53</sup> Therefore, knowing that poor control of diabetes directly affects the immune response and inflammatory processes, these newly diagnosed diabetics have a worse prognosis because they are more susceptible to the harmful effects of untreated diabetes.

Thus, the infection effects seem to be more severe depending on the patient's glycemic control, because hyperglycemia leads to an abrupt systemic metabolic change and an unfavorable hormonal environment worsening the dysregulation of the immune response, characterized by higher levels of

leptin (a proinflammatory adipocin) and lower adiponectin (an anti-inflammatory adipocin).<sup>53</sup> Like that, diabetes patients with uncontrollable plasma glucose levels may have more complications and a worse prognosis.<sup>48</sup> Patients with well-controlled blood glucose presented low frequency of ARDS, acute heart injury and septic shock.<sup>42</sup> Glycemic variability has been shown to be an important indicator and a possible risk predictor for death and other complications in individuals with type 2 diabetes.<sup>42, 48</sup> As they are more severely ill patients, these individuals seem more susceptible to death, and this association between mortality and the presence of diabetes was found in the studies of this systematic review and in a report from the United Kingdom<sup>51</sup> that reported a 2 to 3 times greater risk of diabetes death compared to non-diabetics. Different from hypertension, diabetes is a potential risk factor for death of COVID-19.<sup>48</sup>

Moreover, it is known the immune response may change with advancing age. The elderly has a deficient adaptive immune response compared to the younger ones, given that impairments in T and B cell function occur in this population.<sup>55</sup> Older people also have an excessive production of type 2 cytokines, causing a lack of control in viral replication and longer inflammatory responses, contributing to an unfavorable outcome<sup>46</sup>, for example, most COVID-19 patients with acute kidney injury (AKI) are older<sup>36</sup> probably because of renal vulnerability and cytokines storm. Thus, this deficiency in the immune response may increase mortality in diabetic and hypertensive patients with advanced age.

Gender also plays an important role in the morbidity and mortality of those who are infected with COVID-19. Men are more susceptible to SARS-CoV-2 than women. This can be explained by the fact that male individuals have up to 3 times higher concentration of angiotensin-converting enzyme 2 (ACE-2) than women<sup>23</sup>, and, knowing that ACE-2 is the coronavirus binding site on healthy cells, they end up being more vulnerable<sup>23</sup>. According to a series of cases from the Wuhan Union Hospital<sup>56</sup>, this group has higher morbidity and mortality, increasing the chance of developing severe forms of the disease or dying, regardless of age or susceptibility.

This review has some limitations, primarily due to the nature of the design of the selected studies. The data from case series may be



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biased as the full population is not included. Many chart reviews were based on data of patients that were symptomatic and were hospitalized, and do not represent the population as a whole. We attempted to remove any duplicate data from case reports but it is possible that some case series may have duplicate data with another series or retrospective case review that was included from the same region. In addition, we found a few hypertension's articles reporting the clinical and laboratory findings. More studies about hypertension's effects on the severity of COVID-19 should be done in order to better understand these aspects.

## CONCLUSION

After analyzing the correlated articles about COVID-19 in hypertensive and diabetics, we can point out some highlights: i. Gender plays an important role in morbidity and mortality because men express 3 times more ACE-2; ii. Mortality is

increased in hypertensive and diabetic patients with advanced age due to the immune response natural impairment; iii. Hypertension was the most prevalent comorbidity in hospitalized COVID-19 patients, even between diabetics; iv. Diabetes is an independent risk factor for the prognosis of COVID-19 and hypertension is not an independent factor associated with mortality v. Poorly controlled HBA1C presents an increased risk of bad prognosis vi. Procalcitonin and CRP levels proved to be determinant for the patient's evolution and prognosis. We conclude that hypertension and diabetes were significantly associated with COVID-19 patient's admission to the ICU.

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ANEXOS:

TABELA DE ANALISE DE VIES

[https://docs.google.com/spreadsheets/d/1AqdC1AihMkXHc\\_3Zc6D8CXNZ9WMKYypDk\\_vS0iRwCWg/edit#gid=1321784770](https://docs.google.com/spreadsheets/d/1AqdC1AihMkXHc_3Zc6D8CXNZ9WMKYypDk_vS0iRwCWg/edit#gid=1321784770)