

# MORTALITY IN PATIENTS WITH METABOLIC SYNDROME DURING THE COVID-19 PANDEMIC: A SYSTEMATIC REVIEW

*Mortalidade em pacientes com síndrome metabólica durante a pandemia da COVID-19: uma revisão sistemática.*

Elisabeth Uchoa de Melo<sup>1</sup>, Érika Thienne Lopes da Silva<sup>2</sup>, Gabriela de Sousa Carballosa González<sup>1</sup>, José Kaellyson Barbosa dos Santos Oliveira<sup>1</sup>, Luciana Andrade Tavares<sup>1</sup>, Caroline Araújo<sup>2</sup>

<sup>1</sup>Student from the Programa de Desenvolvimento Institucional de Iniciação Científica, Faculdade de Medicina de Olinda <sup>2</sup>Professor and supervisor from the Programa de Desenvolvimento Institucional de Iniciação Científica, Faculdade de Medicina de Olinda

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## ABSTRACT

The COVID-19 pandemic, the most significant health crisis, was a serious public health issue worldwide. Metabolic comorbidities, such as type 2 diabetes mellitus, hypertension, and obesity, characterized metabolic syndrome and have been associated with increased severity and mortality in COVID-19. The systematic review, conducted following PRISMA statements, investigated the association between mortality in patients with COVID-19 and metabolic syndrome. Cohort, case-control, and cross-sectional studies available in the MEDLINE (EBSCO), Cochrane Library, PubMed, and SciELO databases were included. The search strategy was limited to studies in English, Spanish, and Portuguese from January 2020 to March 2021. Among the 14 studies included, most were published on the MEDLINE (EBSCO) database (64.3%), in English (93.0%), and were cohort studies (57.0%). About 60.0% of the patients were male, with a mean age of 58 years. About 20.0% of patients presented hypertension (25.8%), obesity (20.5%), and type 2 diabetes mellitus (19.1%). The mortality rate was 12.5%, and the occurrence of metabolic syndrome was associated with increased mortality in patients with COVID-19. Further research is needed to elucidate the pathogenic mechanism involved, particularly in hypertensive, diabetic, and obese males, and the development of severe COVID-19.

**Keywords:** complications and mortality, coronavirus infections, glucose metabolism disorders, metabolic syndrome

## RESUMO

A pandemia da COVID-19, responsável pela maior crise sanitária da atualidade, constitui um grave problema de saúde pública mundial. Comorbidades metabólicas, a exemplo da diabetes mellitus tipo 2, hipertensão arterial e obesidade, caracterizam a síndrome metabólica e têm sido associadas às formas graves da doença e óbito. Investigamos a mortalidade em pacientes com COVID-19 e a sua associação com doenças metabólicas. Trata-se de uma revisão sistemática seguindo a recomendação PRISMA. Foram considerados estudos de coorte, caso-controle e corte seccional. As bases de dados MEDLINE/EBSCO, Cochrane Library, PubMed e SciELO foram consultadas por meio das estratégias limitadas aos idiomas inglês, espanhol e português, no período entre janeiro de 2020 e março de 2021. A partir dessa busca, foram observados 14 artigos. A maioria deles foi publicada na plataforma MEDLINE (64,3%), em inglês (93%), do tipo coorte (57%). Em torno de 60% da população dos estudos selecionados, foi constituída por homens, e a média de idade foi de 58 anos. Observou-se que aproximadamente 20% da população total dos estudos apresentava hipertensão (25,8%), obesidade (20,5%) e diabetes (19,1%). A taxa de mortalidade entre eles foi de 12,5%. A presença de comorbidades metabólicas configurou como um dos fatores associados à mortalidade em pacientes com COVID-19. Estudos futuros são necessários para



determinar com precisão o mecanismo patogênico que envolve esses pacientes, especialmente homens hipertensos, diabéticos e obesos, e o desenvolvimento das formas graves da infecção por COVID-19.

**Palavras-chave:** Síndrome metabólica, Infecção por coronavírus, Transtornos do metabolismo da glicose, Obesidade, Complicações e mortalidade

## INTRODUCTION

In early 2020, reports from China described a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused coronavirus disease 2019 (COVID-19). Initially centered in Wuhan, the virus triggered an epidemic in China and rapidly escalated into a global pandemic<sup>1</sup>. By May 2022, the World Health Organization indicated 357,682 new cases and 523,786,368 confirmed cases of COVID-19, including 6,279,667 deaths worldwide<sup>2</sup>.

The novel coronavirus was identified by the Chinese Center for Disease Control and Prevention in respiratory secretion, explaining its transmission via droplets and aerosols<sup>3</sup>. The disease could be asymptomatic in a significant number of patients or symptomatic, whose symptoms include fever, headache, shortness of breath, myalgia, fatigue, and invasive pneumonic infiltrates in both lungs, as shown by chest X-rays. In some cases, gastrointestinal symptoms, such as diarrhea, also occurred<sup>4</sup>.

Comorbidities were associated with the development of severe COVID-19, with obesity, diabetes mellitus, hypertension, and advanced age being the most frequent risk factors among hospitalized patients with severe clinical outcomes and higher mortality<sup>3,5,6,7</sup>. Additionally, the comorbidities presented similar metabolic alterations that influenced the progression and prognosis of COVID-19<sup>8,9</sup>. Thus, the study aimed to investigate the mortality of patients with COVID-19 and its association with metabolic diseases.

## METHODS

The systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statements<sup>10,11</sup>.

### Study screening and selection strategy

The systematic review included observational

(cross-sectional, case-control, and cohort) and interventional (randomized clinical trials) studies involving humans, available in MEDLINE (EBSCO), Cochrane Library, National Library of Medicine (PubMed), and Scientific Electronic Library Online (SciELO) databases. The search strategy was limited to studies in English, Portuguese, and Spanish from January 2020 (the first studies on COVID-19) to April 2021. The Medical Subject Headings and the Health Sciences Descriptors tools were used as keywords for selecting search terms. The Boolean operators AND and OR refined the search strategy through several combinations. The initial keywords included SARS-CoV-2, COVID-19, coronavirus, metabolic syndrome, metabolic disease, obesity, mortality, hypertriglyceridemia, and diabetes. The eligible studies were identified using the keyword combinations: [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND metabolic syndrome OR metabolic disease], [SARS-CoV-2 OR 2019-nCoV OR covid-19 OR coronavirus AND obesity], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND obesity AND metabolic syndrome OR metabolic disease], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND mortality AND metabolic syndrome], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND obesity AND mortality], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND obesity AND mortality AND metabolic syndrome OR metabolic disease], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND diabetes], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND obesity AND diabetes], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND mortality AND diabetes], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND diabetes AND metabolic syndrome OR metabolic disease], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND hypertriglyceridemia],

[SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND hypertriglyceridemia AND obesity], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND hypertriglyceridemia AND mortality], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND hypertriglyceridemia AND mortality AND obesity], and [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND hypertriglyceridemia AND diabetes].

Short communications, case reports, editorials, and narrative and systematic reviews related to metabolic syndrome and COVID-19 were not included in the review. Additionally, analytical observational studies with duplicated interventions or with undefined criteria for the definition of SARS-CoV-2 infection or metabolic syndrome were excluded.

The methodology of all studies was critically assessed, and the PRISMA statements were followed to meet the systematic review criteria<sup>10,11</sup>.

### Data extraction

The title and abstract were assessed during the initial search, followed by the full-text assessment based on the inclusion and exclusion criteria. The AXIS tool was used to verify the methodological quality of the study design of the included studies. AXIS is a modified assessment tool for cross-sectional studies to systematically evaluate studies and investigate their reliability. The assessment of the studies was conducted independently by the researchers involved in the study.

Two researchers analyzed the studies and extracted data, including study identification (author, year, research location, and study design), data collection characteristics (assessment duration, source of information, and methods for confirming COVID-19 diagnosis), and main outcomes. The researchers were previously trained to ensure consistency in the analysis, and discrepancies were resolved through discussion or consultation with a third researcher.

### Terms definition

Based on the Diabetes International Federation, metabolic syndrome was defined as the presence of obesity (body mass index  $\geq 30$  kg/

m<sup>2</sup>) and at least two additional factors, such as hypertension (systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 85$  mmHg) and type 2 diabetes mellitus<sup>12</sup>.

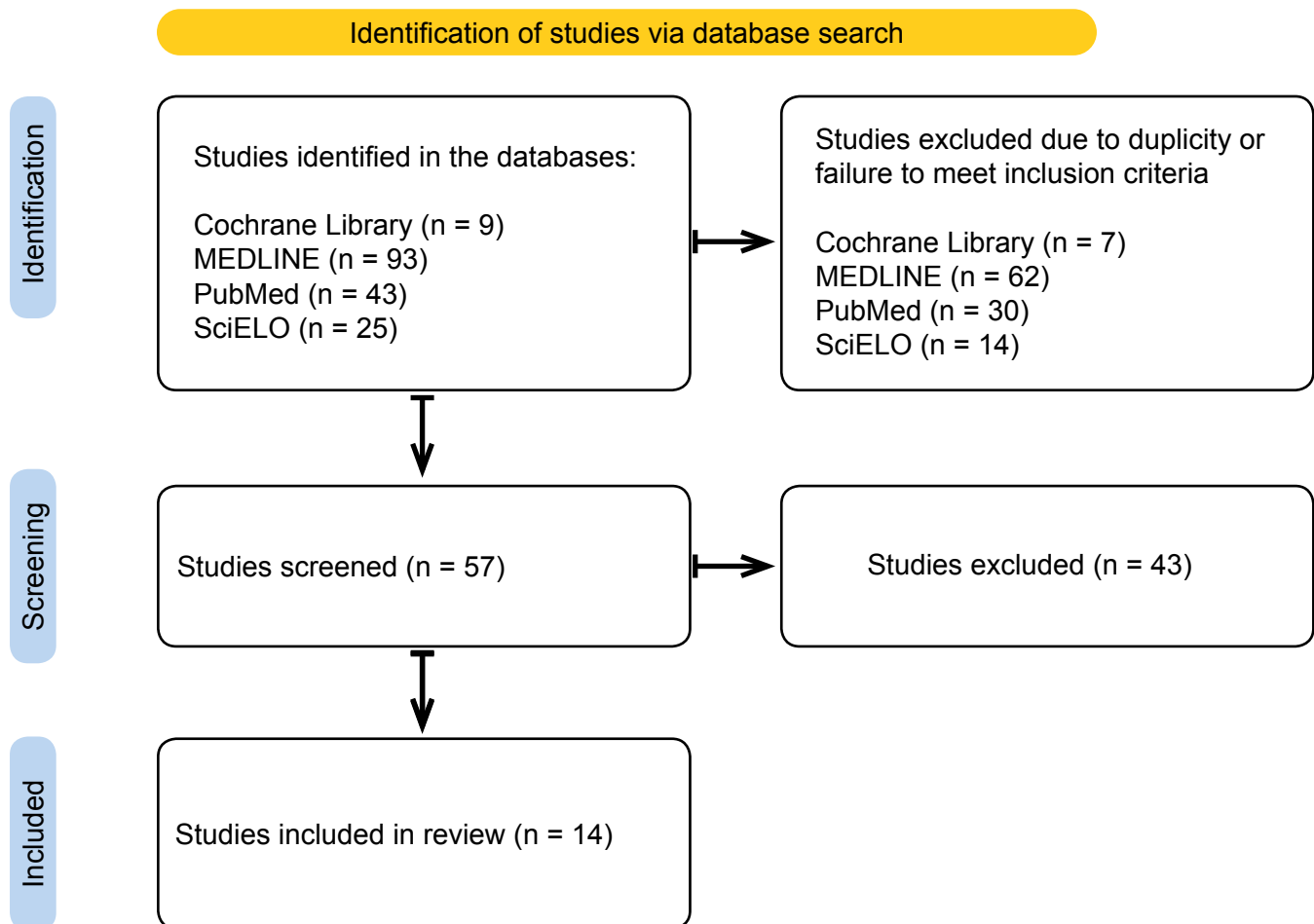
SARS-CoV-2 infection was defined by a positive result from RNA detection via reverse transcription-polymerase chain reaction (RT-PCR) test, following the World Health Organization recommendations<sup>13</sup>.

### Data processing and analysis

Data were stored in a custom database created for the research. The analysis included all studies that present a measure of association (e.g., odds ratio and relative risk). A p-value with a significance level of 5% was adopted.

### Results:

A total of 170 studies were identified in the MEDLINE (EBSCO), Cochrane Library, PubMed, and SciELO databases. Before the initial screening, 113 studies were excluded due to duplication or failure to meet the inclusion criteria. Among the 57 studies selected for screening, 43 were excluded due to undefined criteria for SARS-CoV-2 infection or metabolic syndrome, resulting in 14 studies. The selection process is presented in Figure 1.



**Figure 1.** Flowchart of the systematic review of the studies identified in databases, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statements. n: number of studies.

### General characteristics of the studies and investigated population

**Table 1.** Selected studies: database, location, language, study design, and objectives.

Authors/Year	Database	Country	Language	Study design	Aims
Ciceri F et al. (2020) <sup>14</sup>	Pubmed	Italy	English	Cohort	To describe clinical, demographic, radiologic, and laboratory characteristics, clinical outcomes, and mortality risk factors of patients with COVID-19 in a university hospital in Milan, Italy
Pantea Stoian A et al. (2020) <sup>15</sup>	Pubmed	Romania	English	Cross-sectional retrospective	To investigate the association between mortality and comorbidities, gender, age, and hospital-acquired pneumonia using statistical methods
Ruiz-Quiñonez JA et al. (2021) <sup>7</sup>	Medline	Mexico	English	Cross-sectional retrospective	To assess the demographic and clinical characteristics, and pharmacological treatment of patients who died from COVID-19 in southern Mexico
Rodríguez-Zúñiga MJM et al. (2020) <sup>16</sup>	Scielo	Peru	English	Cohort retrospective	To describe the main factors associated with mortality in a cohort of patients hospitalized with SARS-CoV-2 pneumonia in a public hospital in Lima, Peru
Akbariqomi M et al. (2020) <sup>17</sup>	Pubmed	Iran	English	Cross-sectional retrospective	To describe clinical and epidemiological characteristics, and outcomes of hospitalized patients with COVID-19 with or without diabetes mellitus
Monteiro AC et al. (2020) <sup>18</sup>	Medline	USA	English	Cohort retrospective	To describe the development of respiratory failure in COVID-19 and explore factors associated with the risk of invasive mechanical ventilation.
Thomson RJ et al. (2020) <sup>19</sup>	Medline	United Kingdom	English	Cohort	To understand the characteristics of hospitalized patients in intensive care units in the United Kingdom to inform clinical decision-making, research, and planning for future waves of infection
Kaeuffer C. et al. (2020) <sup>9</sup>	Medline	France	English	Cohort	To identify predictive risk factors for severe COVID-19 and mortality in France
Ebinger JE et al. (2020) <sup>20</sup>	Medline	USA	English	Cross-sectional retrospective	To determine the demographic and clinical characteristics associated with increased severity of COVID-19 infection
Rodríguez-Molinero A et al. (2020) <sup>21</sup>	Medline	Spain	English	Cohort	To analyze the relationship between COVID-19 prognosis, disease presentation, pre-existing pathologies, and chronic treatments
Kammar-García A et al. (2020) <sup>22</sup>	Medline	Mexico	English	Cross-sectional retrospective	To assess the impact of comorbidities on the mortality rate and the occurrence of adverse events in patients with SARS-CoV-2 in Mexico
Nachega JB et al. (2020) <sup>23</sup>	Medline	Congo	English	Cohort retrospective	To describe clinical, laboratory characteristics, and outcomes of hospitalized patients with COVID-19 and differentiate them from other non-African patients
Wang S et al. (2020) <sup>24</sup>	Medline	China	English	Cohort retrospective	To describe the clinical characteristics of patients with COVID-19 in Fujian Province, China
Saldías Peñafiel F et al. (2020) <sup>25</sup>	Scielo	Chile	Spanish	Cross-sectional	To describe the clinical characteristics, risk factors, and predictors of hospitalization in adult patients treated for acute respiratory infections associated with SARS-CoV-2

USA: United States of America

**Table 2.** Selected studies: sample size, number of male patients, mean age, obesity, systemic arterial hypertension (SAH), type 2 diabetes mellitus (T2DM), and mortality

Authors/Year	Sample size	Male n (%)	Age (Mean)	Obesity n (%)	SAH n (%)	T2DM n (%)	Mortality n (%)
Ciceri F et al. (2020)14	410	299 (72.9%)	65	78 (19%)	203 (49.5%)	61 (14.9%)	95 (23.2%)
Pantea Stoian A et al. (2020)15	432	282 (65.3%)	67	53 (12.3%)	162 (37.5%)	153 (35.4%)	432 (100%)
Ruiz-Quiñonez JA et al. (2021)7	185	95 (51.3%)	59	81 (43.8%)	110 (59.4%)	112 (60.5%)	185 (100%)
Rodríguez-Zúñiga MJM. et al. (2020)16	122	86 (70.5%)	56	122 (100%)	16 (13.1%)	21 (17.2%)	45 (36.6%)
Akbariqomi M et al. (2020)17	595	401 (67.4%)	55	176 (29.6%)	172 (28.9%)	148 (24.9%)	65 (10.9%)
Monteiro AC et al. (2020)18	112	75 (67%)	61	41 (36.6%)	61 (54.5%)	73 (65.2%)	41 (36.6%)
Thomson RJ. et al. (2020)19	156	112 (71.8%)	62	89 (57%)	81 (51.9%)	52 (33.3%)	38 (24.3%)
Kaeuffer C et al. (2020)9	1045	612 (58.6%)	66	351 (33.6%)	548 (52.4%)	264 (25.3%)	195 (18.7%)
Ebinger JE et al. (2020)20	442	256 (57.9%)	53	71 (16.1%)	161 (36.4%)	84 (19%)	11 (2.5%)
Rodríguez-Molinero A et al. (2020)21	418	238 (56.9%)	65	74 (17.7%)	217 (51.9%)	99 (23.7%)	79 (18.9%)
Kammar-García A et al. (2020)22	13.842	7989 (57.7%)	47	2793 (20.2%)	2969 (24.4%)	2502 (18.1%)	1302 (9.4%)
Nachega JB et al. (2020)23	766	500 (65.27%)	58	39 (5.1%)	194 (25.3%)	107 (14%)	102 (13.3%)
Wang S et al. (2020)24	199	105 (52.8%)	46	7 (3.5%)	31 (15.6%)	15 (7.5%)	1 (0.5%)
Saldías Peñafiel F et al. (2020)25	1022	507 (49.6%)	41	36 (3.5%)	128 (12.5%)	46 (4.5%)	3 (0.3%)

n: number of patients; %: percentage; SAH: systemic arterial hypertension; T2DM: type 2 diabetes mellitus.

Tables 1 and 2 present the main characteristics of the selected studies and the studied population, respectively. Most studies were published in the MEDLINE (EBSCO) (64.3%), in English (93.0%), and used a cohort (57.0%) and retrospective design (64.3%). The studies were conducted across four continents, excluding Oceania, with the Americas (43.0%) and Europe (36.0%) being the most represented. All studies aimed to describe the clinical and epidemiological characteristics of patients with

COVID-19 and factors associated with mortality, including comorbidities defining metabolic syndrome (Table 1). About 60.0% of the study population were male. The mean age ranged from 41 to 67 years, with 58 years in most studies. About 20.0% of the patients had hypertension (25.8%), obesity (20.5%), and type 2 diabetes mellitus (19.1%). The mortality rate was 12.5% (Table 2), and the prevalence of metabolic comorbidities was associated with mortality in patients with COVID-19 (Table 3)..

**Table 3.** Selected studies: Association of metabolic comorbidities and mortality in COVID-19 patients

Authors/Year	Sample size	Mortality n (%)	Obesity n (%)	OR (CI 95%)	SAH n (%)	OR (CI 95%)	T2DM n (%)	OR (CI 95%)
Ciceri F et al. (2020) <sup>14</sup>	410	95 (23.2%)	78 (19%)	-	203 (49.5%)	-	61 (14.9%)	-
Pantea Stoian A et al. (2020) <sup>15</sup>	432	432 (100%)	53 (12.3%)	1.3* (0.84 - 2.01)	162 (37.5%)	2.09 (1.56 - 2.81)	153 (35.4%)	0.70 (0.49 - 0.99)
Ruiz-Quiñonez JA et al. (2021) <sup>7</sup>	185	185 (100%)	81 (43.8%)	-	110 (59.4%)	-	112 (60.5%)	-
Rodríguez-Zúñiga MJM et al. (2020) <sup>16</sup>	122	45 (36.6%)	122 (100%)	1.01 (1.01 - 1.05)	16 (13.1%)	1.68 (1.09 - 2.56)	21 (17.2%)	-
Akbariqomi M et al. (2020) <sup>17</sup>	595	65 (10.9%)	176 (29.6%)	-	172 (28.9%)	-	148 (24.9%)	-
Monteiro AC et al. (2020) <sup>18</sup>	112	41 (36.6%)	41 (36.6%)	5.82 (1.74 - 19.48)	61 (54.5%)	2.28* (0.68 - 7.61)	73 (65.2%)	1.71* (0.55 - 5.37)
Thomson RJ et al. (2020) <sup>19</sup>	156	38 (24.3%)	89 (57%)	3.06 (1.16 - 8.74)	81 (51.9%)	-	52 (33.3%)	-
Kaeuffer C et al. (2020) <sup>9</sup>	1045	195 (18.7%)	351 (33.6%)	1.4* (0.7 - 2.5)	548 (52.4%)	0.6 (0.3 - 0.9)	264 (25.3%)	1.7* (1.0 - 2.7)
Ebinger JE et al. (2020) <sup>20</sup>	442	11 (2.5%)	71 (16.1%)	1.95 (1.11 - 3.42)	161 (36.4%)	1.19* (0.71 - 1.99)	84 (19%)	1.77 (1.03 - 3.03)
Rodríguez-Moliner A et al. (2020) <sup>21</sup>	418	79 (18.9%)	74 (17.7%)	0.09* (0.19 - 3.66)	217 (51.9%)	1.59* (0.74 - 3.43)	99 (23.7%)	1.71* (0.90 - 3.26)
Kammar-García A et al. (2020) <sup>22</sup>	13.842	1302 (9.4%)	2793 (20.2%)	-	2969 (24.4%)	-	2502 (18.1%)	-
Nachega JB et al. (2020) <sup>23</sup>	766	102 (13.3%)	39 (5.1%)	2.30 (1.24 - 4.27)	194 (25.3%)	1.00* (0.62 - 1.61)	107 (13.9%)	1.10* (0.66 - 1.81)
Wang S et al. (2020) <sup>24</sup>	199	1 (0.5%)	7 (3.5%)	-	31 (15.6%)	3.43 (1.05 - 11.1)	15 (7.5%)	6.93 (1.64 - 29.2)
Saldías Peñafiel F et al. (2020) <sup>25</sup>	1022	3 (0.3%)	36 (3.5%)	-	128 (12.5%)	-	46 (4.5%)	-

n: number of patients; SAH: systemic arterial hypertension; T2DM: type 2 diabetes mellitus; OR: odds ratio; CI: confidence interval.

## DISCUSSION

COVID-19 disease, currently dispersed, has caused more than six million deaths worldwide<sup>2</sup>, becoming a severe public health issue. Some comorbidities, such as hypertension, type 2 diabetes mellitus, and obesity, have been associated with severe forms of COVID-19<sup>7,9</sup>. The pathophysiology of cardiometabolic comorbidities associated with COVID-19 remains unclear in the literature; however, endothelial dysfunction has been noted among these conditions<sup>26</sup>. Besides the vascular endothelium, the angiotensin-converting enzyme 2 has also been targeted due to its high expression in cardiac and respiratory tissues, potentially contributing to the occurrence of symptoms and complications<sup>26,27</sup>.

The mortality rate among the analyzed studies was 12.5%, consistent with retrospective studies conducted in Iran, Mexico, and Congo<sup>17,22,23</sup>. About 75.0% of the included studies, which presented a significant odds ratio ranging between 3.43 and 1.68, showed a positive association between the presence of hypertension and mortality in patients with COVID-19<sup>15,16,24</sup>. Dysregulated blood pressure in this population, evidenced by high systolic and diastolic blood pressure (139 mmHg and 89 mmHg, respectively)<sup>28</sup>, increases inflammatory response and oxidative stress<sup>29</sup> due to elevated levels of cytokines, proteins, and circulating free radicals. Given the crucial role of endothelial cells in vascular homeostasis and organ perfusion, the relationship between endothelial dysfunction and the development of severe COVID-19 is particularly relevant.

However, a cohort study involving 1,045 patients in France identified an inverse association between hypertension and mortality due to the protective effect of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, which were used by 60% of study patients<sup>9</sup>.

In Brazil, obesity was the main comorbidity associated with death in patients under 60 years, regardless of COVID-19 serological status<sup>30</sup>. Furthermore, in patients with positive COVID-19 serology, obesity was also associated with increased mortality<sup>16,18-20,23</sup>. A possible explanation was the increased oxidative stress caused

by the synthesis of inflammatory substances (e.g., interleukins and adipocytes) due to excessive fat deposits, particularly in the abdominal region<sup>31</sup>. Combined with COVID-19, this condition exacerbated the inflammatory effect<sup>32</sup> and impacted the morbidity and mortality of patients with obesity. Furthermore, adipose tissue was considered a potential site for the SARS-CoV-2 replication and elimination<sup>23,33</sup>.

The impaired glucose metabolism during chronic hyperglycemia, due to insulin resistance, damaged various target organs essential for maintaining homeostasis, such as blood pressure, lipid metabolism, and the alveolar gas exchange, already impaired by COVID-19<sup>34</sup>. Hyperglycemia also hampered the innate immune response and adaptive lymphomonocytic cellular immunity, which are crucial in the immune reaction to COVID-19 and other opportunistic pathogens<sup>35</sup>. Smith et al.<sup>6</sup> analyzed the clinical characteristics of hospitalized patients with COVID-19 and observed orotracheal intubation, mainly in patients with diabetes mellitus. This finding corroborated the association between impaired glucose metabolism and worse outcomes in hospitalized patients with COVID-19<sup>6</sup>, which was also described in the present study<sup>20,24</sup>. However, a study with Romanian patients described a protective effect (OR = 0.70; CI 95% = 0.49 – 0.99) related to mortality, possibly biased by the inclusion of patients with type 1 diabetes mellitus and unspecified diabetes mellitus<sup>15</sup>.

Mortality in patients with COVID-19 was high when associated with metabolic comorbidities, such as hypertension, type 2 diabetes mellitus, and obesity. Metabolic syndrome is a complex disorder characterized by central fat deposition and insulin resistance<sup>36</sup>. In this context, a direct association seems to exist between the inflammatory process related to metabolic comorbidities and the immune system, leading to an impaired ability to combat infections and their complications. Prospective studies are needed to accurately determine the pathogenic mechanism, particularly in hypertensive, diabetic, and obese males, and in the development of severe COVID-19.

**Conflict of interest:** The authors declare no conflict of interest.



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