Metabolic syndrome and the gravity of COVID-19: an integrative review

Síndrome metabólica e a gravidade da COVID-19: uma revisão integrativa

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ABSTRACT: COVID-19 disease caused by the SARS-CoV-2 coronavirus (Coronavirus-2 severe acute respiratory syndrome) represents a global public health challenge. Evidence presented looking that feature components of metabolic syndrome tend to have a worse prognosis. Metabolic syndrome is defined as a set of metabolic disorders that include insulin resistance, dyslipidemia, central obesity and hypertension, which are risk factors for the development of several chronic diseases, including type 2 diabetes and cardiovascular diseases. The aim of the present study was to integratively review the literature on the impact of metabolic syndrome and its components on the outcome of patients with COVID-19. This study is an integrative literature review. Articles from 2020 and 2021 were selected in Pubmed and the Virtual Health Library using the descriptors: "COVID-19", "metabolic syndrome", "adults". The inclusion criteria adopted were: primary articles performed with adults; available in full; in Portuguese, English and Spanish. Initially 372 studies were selected, then 101 articles by reading the titles and after obtaining 28 by abstracts, of which, after reading in full, nine were elected to compose the sample. Finally, the interpretation of the results and writing of the article were performed. The study found that the association of metabolic syndrome with COVID-19 lead to a worse clinical outcome. The presence of factors that make up the metabolic syndrome are related to an increased likelihood of mechanical ventilation compliance, intensive care unit treatment, respiratory failure, pressure ulcers, and increased risk of mortality. On the other hand, it is shown that HDL can be used as a risk marker for severe COVID-19 outcomes and a triglycerides / HDL-c ratio as a prognostic marker of severity. Furthermore, a possible multimorbidity present in patients with advanced metabolic syndrome in this study corroborates the importance of controlling its components through educational actions, goals and therapeutic controls, through the multidisciplinary team, to provide a better quality of life.

KEYWORDS: Covid 19; Metabolic syndrome, adults.

RESUMO: A doença COVID-19 provocada pelo coronavírus SARS-CoV-2 (síndrome respiratória aguda grave Coronavírus-2) representa um desafio à saúde pública global. Evidências mostram que indivíduos que apresentam os componentes da síndrome metabólica tendem a ter um pior prognóstico. A síndrome metabólica é definida como conjunto de distúrbios metabólicos que incluem resistência à insulina, dislipidemia, obesidade central e hipertensão, os quais são fatores de risco para o desenvolvimento de várias doenças crônicas, entre elas o diabetes tipo 2 e doenças cardiovasculares. O objetivo do presente estudo foi revisar integrativamente a literatura sobre o impacto da síndrome metabólica e seus componentes no desfecho dos indivíduos portadores de COVID-19. O presente estudo trata-se de uma revisão integrativa de literatura. Foram selecionados artigos de 2020 e 2021 no Pubmed e Biblioteca Virtual em Saúde usando os descritores: "COVID-19", "síndrome metabólica" e "adultos". Os critérios de inclusão adotados foram: artigos primários realizados com adultos; disponíveis na íntegra; nos idiomas português, inglês e espanhol. Inicialmente foram selecionados 372 estudos, em seguida 101 artigos pela leitura dos títulos e após obteve-se 28 pelos resumos, dos quais, após a leitura na íntegra elegeram-se nove para compor a amostra. Por fim, realizou-se a interpretação dos resultados e redação do artigo. Os achados deste estudo concluíram que a associação da síndrome metabólica à COVID-19 acarretam em um pior desfecho clínico. A presença de fatores que compõem a síndrome metabólica esteve relacionada à maior probabilidade de ventilação mecânica, tratamento na unidade de terapia intensiva, falha respiratória, úlceras de pressão e maior risco de mortalidade. Por outro lado, apresentou-se que o HDL pode ser utilizado como marcador de risco para desfechos COVID-19 grave e a relação triglicerídeos/HDL-c como marcador de prognóstico de gravidade. Ademais, a possível multimorbidade presente em pacientes com síndrome metabólica descrita neste estudo corrobora a importância do controle de seus componentes através de ações educativas, metas e controles terapêuticos, por meio da equipe multidisciplinar, para proporcionar uma melhor qualidade de vida.

PALAVRAS-CHAVE: Covid 19; Síndrome metabólica, adultos.

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INTRODUCTION

At the end of 2019, a Chinese province reported cases of a disease caused by the coronavirus, characterized by pneumonia of unknown cause, named Severe Acute Respiratory Syndrome - Coronavirus 2 (SARS-CoV-2) or COVID-19. With its unstable behavior, it has spread rapidly throughout China and other countries around the world and due to its high infecting capacity, it has become a pandemic and a public health emergency[1,2].

The evolution of the disease and clinical manifestations can vary from asymptomatic or mild to severe forms of respiratory failure that can lead to death. There is evidence that the pathogen affects several systems in addition to the respiratory system. Initially, diagnosing this new disease was complex due to the diversity of symptoms and the severity of the condition. Studies have observed a high risk of serious illness in infected patients with underlying health conditions[1,2,3].

Many studies have emerged with the aim of understanding risk factors, treatment protocols and the need for resources to combat the disease. According to data compiled from the COVID-19 Associated Hospitalization Surveillance Network (COVID-NET), the most frequent comorbidities in hospitalized COVID-19 patients in the United States were hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (DM) (28.3%) and cardiovascular disease (27.8%)[2,4].

In view of the above, metabolic syndrome (MS) is a common denominator for these comorbidities since it is defined as a set of metabolic disorders including insulin resistance, dyslipidemia, central obesity and hypertension, which are risk factors for the development of type 2 diabetes and cardiovascular diseases[3].

Given the alarming public health concerns and high mortality associated with COVID-19, it is important to identify possible factors associated with a worse prognosis. In this context, the aim of this study is to carry out an integrative review of the scientific literature regarding the association between metabolic syndrome and the severity of COVID-19, with the aim of understanding this relationship with the disease, clarifying existing scientific evidence and contributing to future research.

METHODOLOGY

This study was carried out using the integrative review method, which is exploratory in nature, surveying and analyzing the literature. In the first stage, the guiding research question was defined: "What is the association between metabolic syndrome and the severity of COVID-19?" The PICO strategy was used to develop the research question: Population: adults with COVID-19; Intervention: components of metabolic syndrome as an aggravating factor; Comparison: with and without metabolic syndrome; Outcome: severity of COVID-19.

Articles were selected in September 2021 from the following databases: National Library of Medicine National Institutes of Health (PubMed) and Virtual Health Library (VHL).

The DECs/MESH health descriptors used were: (COVID-19) OR (Metabolic Syndrome) OR (Adults) in Portuguese, English and Spanish.

The inclusion criteria were complete original articles published in the period from 2020 to 2021 in Portuguese, English and Spanish, and the exclusion criteria were theses, dissertations, editorials, case and review studies and duplicate studies in the databases.

To collect the data, an adapted tool was used to organize and summarize the studies, generating a synthesis of the information obtained[5]. The variables used were: first author, year, country, title, type of study and main results.

The process of searching and analyzing the studies was carried out by three researchers. Initially, 372 studies were selected, then 101 articles by reading the titles, and after reading the abstracts, 28 articles were obtained, of which, after a full reading, eight were chosen to constitute the sample. Finally, the results were interpreted, and the article was composed.

The PRISMA 2020 *statement: An updated guideline for reporting systematic reviews*[6] was used to cover the four stages of the review, which are summarized in Figure 1.
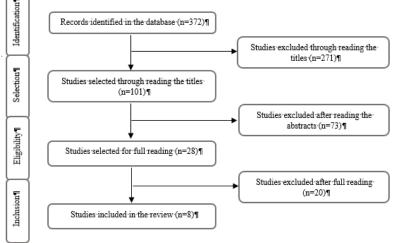

Figure 1 - Flowchart of the process of identification, selection, eligibility, and inclusion of studies for this review.

RESULTS

Study	Reference	Database	Origin	Study type	Results
1	Cho DH et al[7]. Metabolic syndrome and the risk of COVID-19 infection: A nationwide population-based case-control study. Nutr Metab Cardiovasc Dis. 2021; 31(9): 2596-2604.	PubMed	Korea	National Cohort	The COVID-19 group included 4,070 individuals and the control group included 27,618; The prevalence of MetS was 24.7% and 24.5% in the COVID-19 and control groups, respectively; Central obesity was associated with a higher risk of COVID-19 infection (OR=1.17; p=0.001); The presence of MetS was significantly associated with severe COVID-19 (OR=1.25; p=0.352); Pre-diabetes/diabetes mellitus was associated with a higher risk of severe COVID-19 (OR=1.61, p=0.001); The risk of severe COVID-19 increased linearly according to the number of metabolic components.
2	Van Zelst et al[8]. Analyses of abdominal adiposity and metabolic syndrome as risk factors for respiratory distress in COVID-19. BMJ Open Respir Res. 2020 7(1):e000792	PubMed	Netherlands	Prospective Observational Cohort	166 hospitalized patients, 52% tested positive for COVID-19; The prevalence of metabolic syndrome did not differ between COVID-19 patients with and without the need for intubation or level of supportive care (37.5% vs 48.4%, p = 0.338); Abdominal adiposity was an independent risk factor for respiratory distress in COVID-19, adjusted for metabolic syndrome, age, gender and body mass index (OR 1.11, p =0.014).
3	Petersen et al[9]. The role of visceral adiposity in the severity of COVID-19: Highlights from a unicenter cross-sectional pilot study in Germany. Metabolism. 2020; 110:154317.	PubMed	Berlin, Germany	Cross-sectional Cohort	Upon evaluating 30 individuals who had an increase in visceral fat area of 10 cm2, there was a 1.37 times greater chance of ICU treatment and a 1.32 times greater chance of mechanical ventilation (adjusted for age and gender) and when abdominal circumference was evaluated, each additional centimeter of circumference was associated with 1.13 times and 1.25 times, respectively.
4	Patel et al[10]. Increasing adiposity and the presence of cardiometabolic morbidity is associated with increased Covid-19-related mortality: results from the UK Biobank. BMC EndocrDisord. 2021 Jul 3;21(1):144.	PubMed	Europe – United Kingdom	Longitudinal Cohort	13,502 participants from the UK Biobank were screened for Covid-19, of which 1,582 were positive and 11,920 negative. Among those who tested positive, 305 died. Men who tested positive for Covid-19 had a higher mortality rate than women and tended to be older. Men who tested positive were more likely to have hypertension, dyslipidemia, arrhythmia, diabetes or angina than women. There was no difference in body mass index between the sexes.

continuation

Study	Reference	Database	Origin	Study type	Results
5	Alamdari et al[11]. The impact of metabolic syndrome on morbidity and mortality among intensive care unit admitted COVID-19 patients. Diabetes Metab Syndr. 2020 Nov-Dec;14(6):1979-1986.	PubMed	Tehran, Iran	Retrospective Cohort	Among all the cases with metabolic syndrome, those with altered abdominal circumference, triglycerides and fasting glucose were at a significantly higher risk of severe complications and mortality from COVID-19 in the ICU. The need for mechanical ventilation, respiratory failure and pressure ulcers were significantly higher in patients with metabolic syndrome, and this risk increased even more in patients with a BMI > 40. The size of the abdominal circumference and fasting glucose were obtained by regressive multivariable logic as an independent prognostic factor for mortality.
6	Alcántara-Alonso et al[12]. High triglyceride to HDL-cholesterol ratio as a biochemical marker of severe outcomes in COVID-19 patients. Clin Nutr ESPEN. 2021 Aug;44:437-444.	PubMed	USA	Longitudinal Cohort	The subjects (n=43) had a mean age of 57 ± 14 years; 55.8% were male, 75% of whom required hospitalization, and 44.2% were female, 58% of whom were hospitalized. The most common comorbidities were type 2 diabetes mellitus (58%) and hypertension (40%). Patients hospitalized and in intensive care had lower HDL blood levels and an increased TG/HDL ratio than those with outpatient treatment and mild/asymptomatic COVID-19. Linear regression analysis showed that the TG/HDL ratio can predict increases in inflammatory factors such as LDH ($p < 0.01$); ferritin ($p < 0.01$) and D-dimer ($p < 0.001$). The logistic regression model indicated that a ≥7.45 TG/HDL ratio predicts the need for invasive mechanical ventilation (OR 11.815; $p < 0.01$).
7	Motaib et al.[13]. Disease Severity Among Patients With COVID-19. Cureus. 2021 5;13(2):e13165.	PubMed	Morocco	Retrospective Observational Cohort	The study population included 107 patients with confirmed COVID-19 infection. Obese patients were admitted to the ICU more than non-obese patients (p=0.035). When adjusting for other risk factors for ICU admission, obesity was an independent risk factor for ICU admission (OR = 5.04). When the association of obesity and being overweight with ICU admission was examined, only obesity was significantly associated (OR = 9.11).
8	Maddaloni et al.[14]. Cardiometabolic multimorbidity is associated with a worse Covid-19 prognosis than individual cardiometabolic risk factors: a multicentre retrospective study (CoViDiab II). Cardiovasc Diabetol. 2020 1;19(1):164.	PubMed	Italy	Observational	354 individuals were assessed; those with diabetes (n=81) compared to those without diabetes (273) had more characteristics associated with chronic obstructive pulmonary disease (COPD). The risk of ICU admission was higher in patients with diabetes, hypertension and COPD.

DISCUSSION

The selected studies indicated a worse clinical outcome in patients infected with SARS CoV-2 who previously had Metabolic Syndrome (MetS). The International Diabetes Federation and American Heart Association guidelines define MetS as comprising at least three of the following risk factors: 1) central obesity; abdominal circumference ≥ 80 cm for women or ≥ 90 cm for men; 2) hypertension: Systolic Blood Pressure (SBP) ≥130 mmHg or Diastolic Blood Pressure (DBP) ≥85 mmHg or use of antihypertensive drugs; 3) low high-density lipoprotein (HDL) level: HDL cholesterol level <50 mg/dL for women or <40 mg/dL for men; 4) high Triglyceride (TG) level: TG level ≥150 mg/dL or use of lipid-lowering drugs; and 5) pre-diabetes/diabetes mellitus: fasting blood glucose (FBG) level ≥100 mg/dL or use of diabetes drugs[7,15,16].

In Korea, a cohort included 4,070 individuals with COVID-19 and 27,618 who tested negative for SARS-CoV-2. In this study, a comparison was made between the groups correlating the presence of MetS and the risk of COVID-19 infection. The prevalence of MetS was 24.7% and 24.5% in the COVID-19 and control groups, respectively. The presence of MetS was found to be associated with the risk of developing severe COVID-19 (OR, 1.25; 95% CI, 0.78-2.00, p= 0.352). Furthermore, when assessing the components of MetS in isolation, it was found that pre-diabetes/diabetes mellitus was associated with a higher risk of severe COVID-19 (OR, 1.61; 95% CI, 1.21-2.13, p= 0.001). In addition, central obesity was significantly associated with a higher risk of COVID-19 infection (OR, 1.17; 95% CI, 1.06-1.28, P = 0.001). Thus, the interference of metabolic components in the face of SARS-CoV-2[7] infection was proven.

An observational cohort study carried out in an emergency room in the Netherlands evaluated the interference of abdominal adiposity and respiratory syndrome on respiratory deterioration and length of hospital stay. It was the first study to report abdominal adiposity as an independent risk factor for respiratory distress in COVID-19 adjusted for metabolic syndrome, age, gender and body mass index. The association between MetS and the severity of COVID-19 infection was investigated - which had never been done before. It was observed that all patients with COVID-19 who met the criteria for MetS were admitted to the hospital ward, while none of the patients without MetS were admitted. However, the results presented do not support a relationship between MetS and an impaired clinical outcome or duration of admission for COVID-19. Also in this study, the results presented support the idea that the leptin-adiponectin ratio was elevated in COVID-19 patients with MetS[8].

In Germany, a cross-sectional cohort of thirty COVID-19 patients with a mean age of 65.6 ± 13.1 years from a medical center showed that an increase in visceral fat area of ten square centimeters was associated with a 1.37 times greater likelihood of treatment in the Intensive Care Unit (ICU) and a 1.32 times greater likelihood of mechanical ventilation (adjusted for age and gender). For upper abdominal circumference, each additional centimeter of circumference was associated with a 1.13 times greater likelihood of ICU treatment and a 1.25 times greater likelihood of mechanical ventilation[9]. In this study, it was reiterated that visceral adipose tissue, which is considered more metabolically active than subcutaneous adipose tissue, is associated with the release of adipokines and pro-inflammatory cytokines, such as tumor necrosis factor, interleukin-6, C-reactive protein and leptin[9,17,18]. In addition, leptin was found to be related to airway reactivity and levels were found to be elevated in severely COVID-19 infected individuals[9,19,20].

Central obesity, which is quantified by the waist-to-hip ratio, is related to mortality associated with COVID-19. To corroborate this, a longitudinal cohort study with 13,502 participants found that individuals with a body mass index (BMI) ≥35 kg/m2 (obese II) had significantly higher odds of COVID-19-related mortality (OR 1.70, 95% CI 1.06-2.74, p <0.05). On the other hand, for each unit increase in BMI, waist-to-hip ratio and body fat percentage, the odds of death among swab-positive participants increased by 1.04 (95% CI 1.01-1.07), 10.71 (95% CI 1.57-73.06) and 1.03 (95% CI 1.01-1.05), respectively (all p <0.05)[10].

In a retrospective cohort study carried out in Iran on 157 patients with COVID-19, those with the described MetS factors (n = 74) had a greater impact on admission to the intensive care unit, with the need for mechanical ventilation, respiratory failure, pressure ulcers and, in addition, had a higher risk of mortality[11].

A longitudinal cohort conducted in the United States with 43 adult patients with a confirmed diagnosis of COVID-19 by quantitative polymerase chain reaction at the beginning of the study and 15 days later, showed that hospitalized and intensive care patients had lower HDL-c blood levels and an increased triglyceride/high-density lipoprotein ratio (Tg/HDL-c) than those with outpatient treatment and mild/asymptomatic COVID-19. Furthermore, the severity of the disease was related to Tg/HDL-c levels, through variables such as lactate dehydrogenase (LDH) values (r=0.356; p<0.05), National Early Warning Score 2 (NEWS 2) (r=0.495; p<0.01); rapid sequential organ failure assessment (qSOFA) (r = ,538; p <0.001); increased need for oxygen support (r=0.447; p <0.01) and need for mechanical ventilation (r=0.378; p <0.05). Therefore, the study concluded that HDL-c can be used as a risk marker for severe COVID-19 outcomes and the Tg/HDL-c ratio as a new biochemical marker of severe prognosis and need for invasive mechanical ventilation in patients with COVID-19[12].

In Morocco, a retrospective observational study,

which included 107 hospitalized patients with confirmed COVID-19 infection, found that obese patients were admitted to the ICU more than non-obese patients (p=0.035). In addition, patients with severe COVID-19 were more likely to have other comorbidities, such as hypertension and diabetes. However, when the association of obesity and being overweight with ICU admission was examined, only obesity was significantly associated (OR = 9.11). Since this condition may have been determined by the inflammatory process, greater expression of ACE2 receptors in adipose tissue, which are described as an important pathway in the spread of COVID-19.[13]

The analysis of the interference of multimorbidity associated with COVID-19 was verified in a retrospective multicenter study carried out in Italy, where the objective was to verify whether cardiometabolic multimorbidity (defined as ≥ 2 of the three risk factors of diabetes, hypertension and dyslipidemia) was related to the primary outcome composed of mechanical ventilation, admission to the intensive care unit (ICU) or death in patients infected with SARS-CoV-2. Statistical analysis showed that the primary outcome increased with an increase in the number of cardiometabolic risk factors, regardless of age, gender and COPD[14].

MetS can be considered a risk factor and worse clinical outcome for COVID-19 since the association of unfavorable conditions, such as abdominal adiposity, dyslipidemia, hypertension, pre-diabetes/diabetes mellitus condition the body to a pro-inflammatory state, increasing the risk of mechanical ventilation and/or treatment in the ICU. It is therefore important to highlight the multimorbidity described and presented in this study, corroborating the importance of the multidisciplinary team in presenting therapeutic goals and strategies aimed at controlling these diseases.

CONCLUSION

The findings of this study conclude that the association of metabolic syndrome with COVID-19 leads to a worse clinical outcome. The presence of factors that make up the metabolic syndrome was related to a greater likelihood of mechanical ventilation, ICU treatment, respiratory failure, pressure ulcers and a higher risk of mortality. On the other hand, it was shown that HDL can be used as a risk marker for severe COVID-19 outcomes and the Tg/HDL-c ratio as a prognostic marker of severity. In addition, the possible multimorbidity present in patients with metabolic syndrome described in this study corroborates the importance of controlling these individuals, through educational actions, goals and therapeutic controls, through the multidisciplinary team to provide a better quality of life. Finally, the evidence presented in this study helps in the management of patients with MetS affected by COVID-19 and in promotion and prevention measures for possible future events.

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