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OBESITY IN THE CLINICAL EVOLUTION OF PATIENTS WITH COVID-19

OBESIDADE NA EVOLUÇÃO CLÍNICA DE PACIENTES COM COVID-19

OBESIDAD EN LA EVOLUCIÓN CLÍNICA DE PACIENTES CON COVID-19

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ABSTRACT

Objective: to verify the lethality rate of evolution to death by Covid-19 in a group of self-reported obese people and to analyze the associated factors from the database of the e-SUS Notifica portal. **Method:** This descriptive study used secondary data from symptomatic COVID-19 patients treated in Porto Velho, Rondônia, between June 2020 and June 2021. Data were extracted from the e-SUS Notifica system. Statistical analysis included fatality rates and a hierarchical model with three levels of variables. Factors associated with the evolution to death were identified with a p-value ≤ 0.05. **Results:** the results highlight that obesity is a risk factor for death in patients with COVID-19 and that other factors, such as advanced age and the presence of comorbidities, also increase the risk of mortality from COVID-19 in obese patients. **Conclusion:** these findings emphasize the need for prevention and control of obesity and its comorbidities to minimize the impact of COVID-19 on the obese population.

Descriptors: COVID-19; Obesity; Risk factors.

RESUMO

Objetivo: verificar a taxa de letalidade de evolução para óbito por Covid-19 em um grupo de obesos autorrelatados e analisar os fatores associados do banco de dados do portal e-SUS Notifica. **Método:** este estudo descritivo utilizou dados secundários de pacientes sintomáticos de COVID-19 atendidos em Porto Velho, Rondônia, entre junho de 2020 e junho de 2021. Os dados foram extraídos do sistema e-SUS Notifica. A análise estatística incluiu taxas de letalidade e um modelo hierárquico com três níveis de variáveis. Os fatores associados à evolução para óbito foram identificados com um valor de p ≤ 0,05. **Resultados:** os resultados destacam que a obesidade é um fator de risco para o óbito em pacientes com COVID-19 e que outros fatores, como a idade avançada e a presença de comorbidades, também aumentam o risco de mortalidade por COVID-19 em pacientes obesos. **Conclusão:** esses achados enfatizam a necessidade de prevenção e controle da obesidade e de suas comorbidades para minimizar o impacto da COVID-19 na população obesa.

Descritores: COVID-19; Obesidade; Fatores de Risco.

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RESUMEN:
Objetivo: verificar la tasa de letalidad de evolución a muerte por Covid-19 en un grupo de obesos autorreferidos y analizar los factores asociados a partir de la base de datos del portal e-SUS Notifica. **Método:** este estudio descriptivo utilizó datos secundarios de pacientes sintomáticos de COVID-19 atendidos en Porto Velho, Rondônia, entre junio de 2020 y junio de 2021. Los datos fueron extraídos del sistema e-SUS Notifica. El análisis estadístico incluyó tasas de mortalidad y un modelo jerárquico con tres niveles de variables. Los factores asociados a la evolución a muerte se identificaron con un valor de $p \leq 0,05$. **Resultados:** los resultados destacan que la obesidad es un factor de riesgo de muerte en pacientes con COVID-19 y que otros factores, como la edad avanzada y la presencia de comorbilidades, también aumentan el riesgo de mortalidad por COVID-19 en pacientes obesos. **Conclusión:** estos hallazgos enfatizan la necesidad de prevención y control de la obesidad y sus comorbilidades para minimizar el impacto de COVID-19 en la población obesa.
Descriptores: COVID-19; Obesidad; Factores de riesgo.

INTRODUCTION

Chronic Non-Communicable Diseases (CNCDs) are the leading cause of death in adults in Brazil. Obesity, in addition to being considered a chronic disease, is a risk factor for the development of other NCDs, such as diabetes mellitus, hypertension, cardiovascular diseases, dyslipidemia and neoplasms.[1] Since the outbreak of the SARS-CoV-2 infection in December 2019 in Wuhan, China, studies have begun to emerge that link obesity as a risk factor for serious clinical complications in infected individuals.[2]

A study carried out in Brazil evaluated the risk of hospitalization in outpatients with COVID-19 and found that the risk of hospitalization doubled in people with obesity.[3] Obesity has been shown to be a significant risk factor for COVID-19 infection since the first clinical studies carried out in countries such as the United States, China, Italy, France and Mexico.[4] This risk is related to the fact that obesity causes a chronic state of inflammation that can compromise immunity, making obese people more susceptible to contracting infections.[5] In addition, obesity compromises lung function, since it is associated with a decrease in functional capacity, expiratory reserve volume and lung compliance.[4]

In the first quarter of 2021, the state of Rondônia presented an alarming number of positive cases for COVID-19, reaching 187,270 positive cases and 4,143 deaths, making it necessary to request assistance from the Ministry of Health and from states in other regions of the country for the treatment of Rondonian citizens.[5]

However, few studies to date have determined the risk factors for COVID-19 in the general population. Some studies have found that obesity and chronic kidney disease (CKD) are predictors with no statistically significant association with

other chronic conditions[6]. Based on this finding, the following objective was formulated: to verify the lethality rate of evolution to death by COVID-19 in a group of self-reported obese people and to analyze the associated factors from the database of the e-SUS Notifica portal provided by the Health Surveillance Division of the municipality of Porto Velho/RO in 2020/2021.

METHODOLOGY

This is a descriptive study of secondary data from symptomatic COVID-19 patients treated in the municipality of Porto Velho, capital of the state of Rondônia, from June 1, 2020 to June 30, 2021. This study was approved by the Research Ethics Committee of the Federal University of Rondônia, under opinion number 4.630.505 and CAAE 31450620.1.0000.5300 CEP/CONEP.

The information for this study was taken from the database of the e-SUS Notifica portal, provided by the Health Surveillance Division of the municipality of Porto Velho. This system is used to register all individuals suspected of having COVID-19 who have received medical care in the public or private sector and have undergone diagnostic tests, including a specific Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) test, rapid tests to detect the presence of IgG and IgM antibodies, imaging tests (radiography, tomography) or clinical criteria.[6]

From this database, a spreadsheet was created using Microsoft Excel ® software (2010), in which the study sample consisted of positive and negative cases for COVID-19 with notifications between June 1, 2020 and June 30, 2021. The original spreadsheet contained a total of 280,885 notifications, 1338 of which contained self-reported obesity. After applying filters (state of Rondônia), (municipality Porto Velho), (date of birth before 2000), 811 notifications remained to make up the sample number for this study.

We opted for a power (1 - β) of 99% (β = 2.2%) and a confidence level of 95% (α= 5%) to detect areas under the Receiver Operating Characteristic (ROC) curve equal to or greater than 0.50 as significant. The inclusion criteria were self-reported obesity, residents in the municipality of Porto Velho/RO and age over 20 years. The exclusion criteria were notifications not marked as obesity, under 20 years old and not living in Porto Velho. The age outcome was divided according to the Papalia, Olds and Feldman classification into young adult (20 to 40 years old), middle-aged (41 to 60 years old) and elderly (over 60 years old).

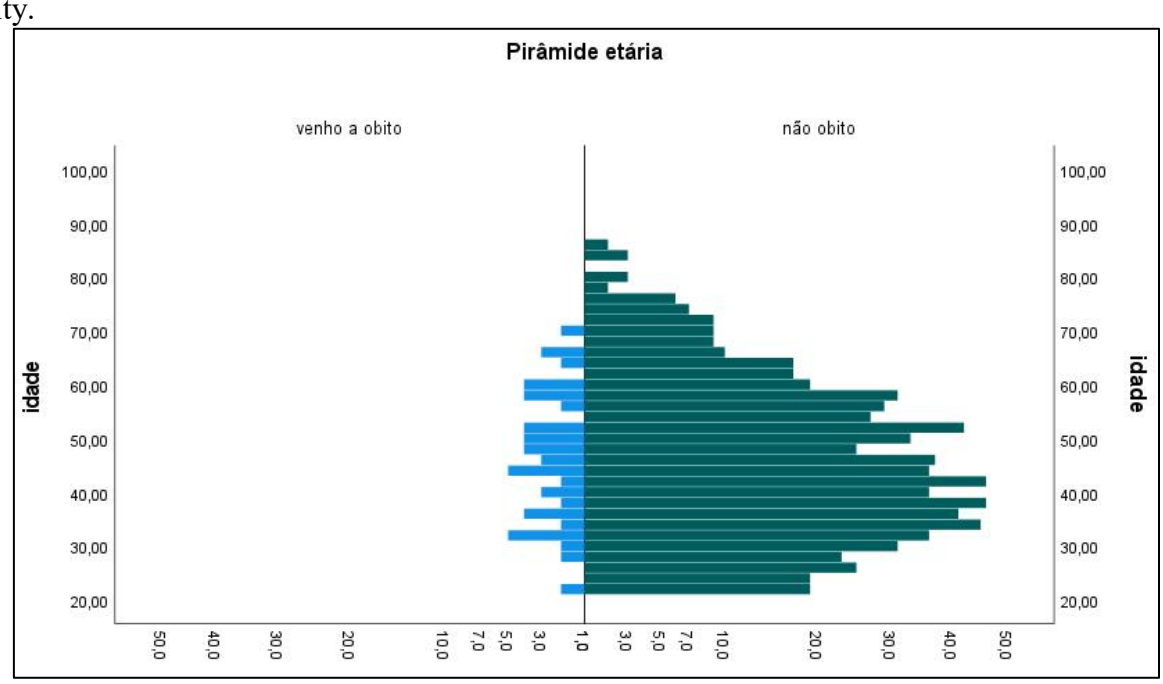
The data was statistically analyzed using the StataTM 11.0 program, using the svy module. Lethality rates (CFR%) and their respective 95% confidence intervals

were calculated. The adjusted analysis followed a hierarchical model with three levels: the first level included sociodemographic variables (gender and age), the second included symptoms (dyspnea and taste disorders) and the third comorbidities (respiratory, cardiac, diabetes and kidney disease). All variables were analyzed in the adjusted model, and only those with a p-value < 0.20 were retained. Factors associated with death from COVID-19 were those with a p-value ≤ 0.05.

RESULTS

The sample consisted of 811 reports of COVID-19 deaths in self-reported obese individuals, of both sexes, with a mean age of 44.60 ± 13.78 years (ranging from 20.00 to 89.00 years). Figure 1 shows the age distribution of COVID-19 deaths in self-reported obese individuals.

Figure 1 - Age distribution of deaths from Covid-19 cases in individuals with self-reported obesity.



Source: authors (2023).

Lethality rates (CFR%) were higher in females (6.72%), in the elderly (>60 years) (20.0%), in individuals with symptoms of dyspnea (14.49%) and taste disorders (9.77%), and in people with respiratory (30.55%), cardiac (15.76%), diabetes (16.50%) and renal (33.33%) comorbidities (see Table 1).

Table 1. Characterization of **progression to death** from COVID-19 in a self-reported obese group, according to sociodemographic variables, symptoms and comorbidities, 2021.

Variables	COVID-19 CASES			
	Total	Lethality rate (CFR %)		
	n (%)	n	%	p-value (95%CI)
Gender				0,261
Female	669 (60,8)	45	6,72	5,07-8,89
Male	431 (39,2)	24	5,56	3,77-8,15
Age (years)				<0,001
Young adult (20-40 years)	357 (44,0)	15	4,20	2,56-6,81
Middle-aged (41 to 60)	354 (43,6)	32	9,03	6,47-12,48
Elderly (>60 years)	100 (12,3)	20	20,0	13,33-28,88
Dyspnea				<0,001
Yes	269 (33,2)	39	14,49	10,79-19,20
No	541 (66,8)	28	5,17	3,60-7,37
Taste disorders				0,008
Yes	604 (74,5)	59	9,77	7,64-12,39
No	207 (25,5)	8	3,86	1,97-7,43
Respiratory disease				<0,001
Yes	36 (4,4)	11	30,55	18,00-46,85
No	775 (95,6)	56	7,22	5,60-9,26
Heart disease				<0,001
Yes	203 (25,0)	32	15,76	11,39-21,40
No	608 (75,0)	35	5,75	4,16-7,90
Diabetes				0,001
Yes	103 (12,7)	17	16,50	10,56-24,85
No	708 (87,3)	50	7,06	5,39-9,19
Kidney disease				0,025
Yes	6 (0,7)	2	33,33	9,67-70,00
No	805 (99,3)	65	8,07	6,38-10,16

Source: authors (2023).

In the adjusted analysis, some factors were found to be associated with death from COVID-19, including middle age (41 to 60 years) (PR=2.25; 95%CI 1.94-4.23; p=0.012), elderly (>60 years) (PR=5.65; 95%CI 2.77-11.54; p<0.001), presence of dyspnea (PR=3.10; 95%CI 1.84-5.23; p<0.001), presence of taste disorders (PR=2.45; 95%CI 1.13-5.31; p=0.023), respiratory comorbidities (PR=3.12; 95%CI 1.74-5.62; p<0.001), cardiac comorbidities (PR=2.00; 95%CI 1.24-3.23; p=0.005), diabetes (PR=1.66; 95%CI 1.09-2.80; p=0.045) and kidney disease (PR=4.20; 95%CI 1.32-13.38; p=0.015) (as shown in Table 2).

Table 2. Crude and adjusted analysis of factors associated with death from COVID-19 in a self-reported obese group, according to sociodemographic variables, symptoms and comorbidities, 2021.

Variables	Raw model PR (95%CI)	p-value	Adjusted Model PR (95%CI)	p-value
Level 1 Demographic				
Level 1				
Gender				
Male	1		1	
Female	1,19 (0,73-1,92)	0,486	1,09 (0,68-1,75)	0,712
Age (years)				
Young adult (20-40 years)	1		1	
Middle-aged (41 to 60)	2,67 (1,20-4,26)	0,011	2,25 (1,94-4,23)	0,012
Elderly (>60 years)	5,70 (2,78-11,62)	<0,001	5,65 (2,77-11,54)	<0,001
Level 2				
Dyspnea				
No	1		1	
Yes	3,11 (1,87-5,17)	<0,001	3,10 (1,84-5,23)	<0,001
Taste disorders				
No	1		1	
Yes	2,69 (1,26-5,73)	0,010	2,45 (1,13-5,31)	0,023
Level 3				
Respiratory disease				
No	1		1	
Yes	4,22 (2,43-7,35)	<0,001	3,12 (1,74-5,62)	<0,001
Heart disease				
No	1		1	
Yes	2,74 (1,74-4,30)	<0,001	2,00 (1,24-3,23)	0,005
Diabetes				
No	1		1	
Yes	2,34 (1,40-3,89)	0,001	1,66 (1,09-2,80)	0,045
Kidney disease				
No	1		1	
Yes	4,12 (1,30-13,10)	0,016	4,20 (1,32-13,38)	0,015

Source: Prepared by the authors (2023).

DISCUSSION

The results indicated that the lethality rate was higher in women, the elderly over 60, individuals with symptoms of dyspnea and taste disorders, as well as respiratory, cardiac, diabetes and kidney disease comorbidities. Obesity is a public health problem and health risk factor, and COVID-19 has become a global pandemic with rapid transmission, progression and a high lethality rate. As of April 25, 2020, the world has registered more than 2,902,708 cases, with a fatality rate of around 20%.[9]

The most serious risk factors associated with COVID-19, which increase the risk of lethality, are age over 60, diabetes, respiratory and heart disease[10] . In addition, people with obesity associated with these comorbidities have an increased risk of progressing to death from COVID-19, as highlighted in the literature.[11,12] Patients diagnosed with COVID-19 and

comorbidities associated with obesity also have a higher risk of hospitalization, mechanical ventilation and mortality during H1N1 and seasonal influenza pandemics.[13]

An important finding of this study was that the lethality rate was higher in females, contrary to the trend of a higher lethality rate among men.[14] Another study on patients with COVID-19 and high BMI (above 25kg/m^2) classified as overweight showed that the severity of the disease was higher for death, especially among women over 50 with respiratory, cardiac and diabetes comorbidities.[15]

With regard to age group, it was observed that middle-aged people (40 to 60 years old) and people over 60 had lethality rates of 9.03% and 20.0%, respectively. The adjusted model showed a risk of death from COVID-19 of 2.25 (p=0.012) and 5.65 (p<0.001), respectively. This pattern is also observed in the Brazilian population in general.

Special epidemiological bulletin No. 106 on the COVID-19 disease issued by the Ministry of Health shows that the elderly population accounted for 66% of reported cases.[16] This association can be explained by mechanisms such as immunosenescence, which refers to the age-related decline in immunity and involves multi-organ changes. As age advances, so does the incidence of various pathologies associated with immunosenescence. Ageing contributes to the decline of the immune system, increasing the incidence and severity of infectious diseases in the elderly.[17]

This study showed that dyspnea (14.49%) and taste disorders (5.17%) were the symptoms with the highest lethality rate among obese patients (n=811) and remained associated in the adjusted model, with a relative risk (RR) of 3.10 (p<0.001) and 2.45 (p=0.023), respectively. It is worth noting that COVID-19 symptoms can appear between 2 and 14 days after exposure and the average incubation period is around 5.2 days. Transmission of the virus can occur on average seven days after the onset of symptoms, but it can also happen even without the appearance of signs and symptoms.[18]

National data collected during the first month of the pandemic showed that the most common symptoms of COVID-19 include fever, dry cough, dyspnea, sore throat, headache and taste and smell disorders, similar to those found in international literature, with a higher incidence of upper airway symptoms.[19] Among non-hospitalized patients, the following findings were found: cough (73.7%), fever (68.8%), runny nose (37.4%), sore throat (36.2%) and dyspnea (5.6%). Among hospitalized patients, the most common symptoms were fever (81.5%), cough (79.8%), dyspnea (26.1%), sore throat (26.1%) and runny nose (31.1%).[20]

Dyspnea is considered a marker of disease severity and is usually established between 5 and 8 days after the onset of symptoms.[19] In COVID-19, dyspnea is associated with more severe stages of the disease and is considered an independent predictor of morbidity and mortality.[20] Studies have shown a close association between COVID-19 and dyspnea.[17-20]

The study showed that the presence of comorbidities was a risk factor for the COVID-19 fatality rate. The main factors were respiratory diseases (30.55%; PR=3.12; 95%CI 1.74-5.62; p<0.001), heart disease (15.76%; PR=2.00; 95%CI 1.24-3.23; p=0.005), diabetes (16.50%; PR= 1.66; 95%CI 1.09-2.80; p=0.045) and kidney disease (33.3%; PR= 4.20; 95%CI 1.32-13.38; p=0015). The presence of comorbidities increased the risk of death by 10.44 times compared to individuals without comorbidities.

Studies in several countries have also shown the prevalence of comorbidities in patients with COVID-19 infections, especially hypertension, diabetes, respiratory and cardiovascular diseases, and these comorbidities have been correlated as risk factors for severe patients hospitalized for COVID-19, compared to non-severe patients.[18]

Considering the data from the Influenza Epidemiological Surveillance Information System (SIVEP) in Brazil, there were almost 50,000 deaths at the end of August 2020 from unspecified severe acute respiratory syndrome (SARS) because they were not tested for COVID-19.[20] A study of 204 laboratory-confirmed individuals in China, 50.5% at the time of hospitalization had symptoms of respiratory illness.[24] Another study carried out in the Chinese province of Zhejiang with 651 people hospitalized with a diagnosis of COVID-19, 11.4% had respiratory symptoms.[12]

As for cardiovascular diseases, Brazil recorded 8,044 confirmed cases and 324 deaths, with a mortality rate of 4%. The same data indicates that 90% of deaths occurred in people over the age of 60 and 84% of patients had at least one comorbidity, with 51% having cardiovascular disease (CVD) and 37.7% having diabetes.

A meta-analysis carried out in Wuhan, China of 44,672 confirmed cases of COVID-19 showed an overall case fatality rate of 2.3%. However, lethality was higher in individuals with cardiovascular disease (CVD) (10.5%), diabetes (7.3%) and hypertension (6%). In addition, cardiovascular complications resulting from COVID-19 have been reported, such as myocardial injury (20% of cases), arrhythmias (16%), myocarditis (10%), heart failure and shock (up to 5% of cases).[15]

Damage to the cardiovascular system is probably caused by several factors, such as an imbalance between high metabolic

demand and insufficient cardiac reserve, systemic inflammation and thrombogenesis, or direct damage to the heart by the virus.[16] This damage to the cardiovascular system resulting from COVID-19 is more common in patients with cardiovascular risk factors, such as advanced age, hypertension and diabetes, or with previous CVD.[16]

Obesity and excess ectopic fat can be risk factors for severe cases of COVID-19 due to their comorbidities, such as cardiovascular disease, insulin resistance, inflammation of adipose tissue and detrimental effects on lung function. Studies show that obesity-related fatty liver disease increases the risk of severe cases of COVID-19 sixfold.[15]

The most severe cases and deaths from COVID-19 occur in older people and those with comorbidities such as diabetes, cardiovascular disease, hypertension, cancer and chronic lung disease. A meta-analysis of 33 studies involving 16,003 participants showed that patients with diabetes and COVID-19 have a higher risk of severity, with an odds ratio of 2.75 (95% CI: 2.09-3.62; p <0.01) compared to those without diabetes, with a higher risk of mortality, with an odds ratio of 1.90 (95% CI: 1.37-2.64; p <0.01). The prevalence of diabetes in COVID-19 patients was 9.8% (95% CI: 8.7-10.9%), after adjusting for heterogeneity.[16]

Diabetes has already been pointed out in the literature as an independent risk factor for mortality among COVID-19 patients.[14] However, other publications do not confirm this association, making this topic still the subject of debate.[13] A study of 1.122 patients hospitalized in the United States showed that patients with transient hyperglycemia had higher mortality rates and remained hospitalized for longer periods than those with DM.[12] This suggests that acute hyperglycemia alone may be an independent risk factor for COVID-19 mortality, as it affects the immune system more aggressively. People with diabetes have a higher risk of developing serious infections, including COVID-19. The mechanisms proposed to explain this association include exacerbated inflammation, changes in coagulation and immune response, and direct damage by the virus to the pancreatic islet cells responsible for regulating blood glucose.[6]

LIMITATION

This study has some possible limitations that should be considered when interpreting its results. Firstly, the quality of secondary data depends on the accuracy and completeness of the information recorded, and there may be typing errors, missing information or inconsistencies, which could affect the reliability of the results. Finally, the study was conducted in a single municipality, Porto Velho, in the state of Rondônia, which limits the generalization of

the results to other geographical regions or different contexts.

CONCLUSION

Based on the results of this study, which sought to analyze the lethality rate in obese patients with COVID-19, it is possible to conclude that obesity is a significant risk factor for mortality from the disease, especially in patients with associated comorbidities such as diabetes, respiratory and heart disease. In addition, the study showed that obese women had a higher mortality rate than men, contrary to the general trend of higher mortality among males. Age is also an important factor, since older people over 60 had a higher fatality rate than younger individuals.

Symptoms of dyspnea and taste disturbances were also associated with a higher lethality rate in obese patients with COVID-19. These findings highlight the importance of preventive measures and obesity control, as well as special care for obese patients with COVID-19 and associated comorbidities.

REFERENCES

1. Schmidt MI, Duncan BB, Azevedo GS, Menezes AM, Monteiro CA, Barreto SM, et al. Doenças crônicas não transmissíveis no Brasil: sobrecarga e desafios atuais. Lanceta. 2011 [citado em 15 abr 2023]; 377(9781): 1949-61. Disponível em: https://doi.org/10.1016/S0140-6736(11)60135-9.

2. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. Obesity (Silver Spring). 2020 [citado em 15 abr 2023]; 28(7): 1195-1199. Disponível em: https://doi.org/10.1002/oby.22831

3. Szente Fonseca SN, Sousa AQ, Wolkoff AG, Moreira MS, Pinto BC, Takeda CFV, et al. Risk of hospitalization for COVID-19 outpatients treated with various drug regimens in Brazil: Comparative analysis. Travel Med Infect Dis. 2020 [citado em 15 abr 2023] 38: 1477-89. Disponível em: https://doi.org/10.1016/j.tmaid.2020.101906.

4. Silva GM da, Pesce GB, Martins DC, Carreira L, Fernandes CAM, Jacques AE. Obesidade como fator agravante da COVID-19 em adultos hospitalizados: revisão integrativa. Acta paul enferm. 2021 [citado em 18 abr 2023]; 34. Disponível em: https://doi.org/10.37689/acta-ape/2021AR02321.

5. Rondônia. Secretaria de Estado de Saúde. Boletim Epidemiológico diário Coronavírus COVID-19; 2022 [citado em 18 abr 2023]. Disponível em: https://rondonia.ro.gov.br/desrespeito-aos-protocolos-de-saude-gera-aumento-nos-obitos-por-covid-19-em-rondonia-nos-tres-primeiros-meses-de-2021/.

6. Porto Velho. Secretaria Municipal de Saúde. Plano Municipal de Contingência para Resposta às Emergências em Saúde Pública CORONAVÍRUS; 2021 [citado em 18 abr 2023]. Disponível em: https://www.portovelho.ro.gov.br/uploads/arquivos/2020/09/34898/15989786251o-versao-plano-contingencia-coronavirus-pdf.pdf.

7. Porto Velho. Secretaria Municipal de Saúde. Semusa explica novos protocolos de atendimentos a serem adotados a partir da próxima segunda-feira; 2020 [citado em 18

abr 2023] Disponível em: https://www.portovelho.ro.gov.br/pesquisar.
8. Papalia DE, Olds SW, Feldman RD. Desenvolvimento humano. 12 ed. Porto Alegre: Artmed; 2013 [citado em 18 abr 2023].
9. Ministério da Saúde (Brasil). Secretaria de Vigilância em Saúde. Guia de vigilância epidemiológica: emergência de saúde pública de importância nacional pela doença pelo Coronavírus 2019: vigilância integrada de Síndromes Respiratórias Agudas: doença pelo Coronavírus 2019, influenza e outros vírus respiratórios. Brasília, DF: Ministério da Saúde; 2020 [citado em 18 abr 2023]. Disponível em: https://www.saude.gov.br/images/pdf/2020/April/06/GuiaDeVigiEp-final.pdf.
10. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in COVID-19 Patients: a systematic review and meta-analysis. Otolaryngology–Head and Neck Surgery. Otolaryngol Head Neck Surg. 2020 [citado em 21 abr 2023]; 163(1): 3-11. Disponível em: https://doi.org/10.1177/0194599820926473.
11. Lechien JR, Chiesa-Estomba CM, Hans S, Barillari MR, Jouffe L, Saussez S. Loss of smell and taste in 2013 european patients with mild to moderate COVID-19. Ann Intern Med. 2020 [citado em 21 abr 2023]; 173(8): 672-675. Disponível em: https://doi.org/10.7326/m20-2428.
12. Lechien JR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. European Archives of Oto-Rhino-Laryngology, 2020 [citado em 21 abr 2023]; 277(8): 2251-2261. Disponível: https://doi.org/10.1007/s00405-020-05965-1.
13. Romero-Sánchez CM, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. Neurology, 2020 [citado em 21 abr 2023]; 95(8): e1060-e1070. Disponível em: https://doi.org/10.1212/wnl.0000000000009937.
14. Li L quan, Huang T, Wang Y qing, et al. covid-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020 [citado em 21 abr 2023]; 92(6): 577-583. Disponível em: https://doi.org/10.1002/jmv.25757.
15. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: A systematic review and meta-analysis.Int J Infect Dis. 2020 [citado em 21 abr 2023]; 2020(94): 91-5. Disponível em: http://dx.doi.org/10.1016/j.ijid.2020.03.017.
16. Park JJH, Mogg R, Smith GE, Nakimuli-Mpungu E, Jehan F, Rayner CR et al. How COVID-19 has fundamentally changed clinical research in global health. Lancet Glob Health. 2021 [citado em 21 abr 2023]; 9(5): e711-20. Disponível: http://dx.doi.org/10.1016/S2214-109X(20)30542-8.
17. Nikolich-Žugich, J. The twilight of immunity: emerging concepts in aging of the immune system. Nat Immunol. 2018 [citado em 22 abr 2023]; 19, 10–19. Disponível em: https://doi.org/10.1038/s41590-017-0006-x
18. Pan L, Mu M, Yang P, Sun Y, Yan J, Li P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, crosssectional, multicenter study. Am J Gastroenterol [Internet]. 2020 [citado em 22 abr 2023]; 115(5): 766- 73. Disponível em: https://doi.org/10.14309/ajg.0000000000000620.
19. Jin X, Lian J-S, Hu J-H, Gao J, Zheng L, Zhang Y-M, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020 [citado em 22 abr 2023]; 69(6): 1002-9. Disponívem em: https://doi.org/10.1136/gutjnl-2020-320926.
20. Brasil.Ministério da Saúde. Secretaria de Vigilância em Saúde. Boletim Epidemiológico 7– COE Coronavírus – 06 de abril de 2020. Brasília (DF); 2020 [citado

em 22 abr 2023]. Disponível em: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/epidemiologicos/covid-19/2020/boletim-epidemiologico-no-7-boletim-coe-coronavirus.pdf/view

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