

## **Comorbidities and causes of death in SARS-CoV-2-infected patients from the Amazon region**

## **Comorbidades e causas de morte em pacientes infectados com SARS-CoV-2 na região amazônica**

DOI:10.34117/bjdv7n12-186

Recebimento dos originais: 12/11/2021

Aceitação para publicação: 01/12/2021

### **Tárcio Peixoto Roca**

Mestre

Instituição de atuação atual: Fundação Oswaldo Cruz Rondônia  
Endereço completo: Rua da Beira, nº. 7671, BR 364, Km 3,5,  
CEP 76812-245 - Porto Velho, RO, Brasil.  
E-mail: tarcioroca@hotmail.com

### **Suyane da Costa Oliveira**

Mestre

Instituição de atuação atual: Fundação Oswaldo Cruz Rondônia  
Endereço completo: Rua da Beira, nº. 7671, BR 364, Km 3,5,  
CEP 76812-245 - Porto Velho, RO, Brasil.  
E-mail: suyaneoliveira\_enf@hotmail.com

### **Gabriella Sgorlon Oliveira**

Bacharel

Instituição de atuação atual: Fundação Oswaldo Cruz Rondônia  
Endereço completo: Rua da Beira, nº. 7671, BR 364, Km 3,5,  
CEP 76812-245 - Porto Velho, RO, Brasil.  
E-mail: gabriellasgorlon@gmail.com

### **Jackson Alves da Silva Queiroz**

Especialista

Instituição de atuação atual: Fundação Oswaldo Cruz Rondônia  
Endereço completo: Rua da Beira, nº. 7671, BR 364, Km 3,5,  
CEP 76812-245 - Porto Velho, RO, Brasil.  
E-mail: queiroz.jas@gmail.com

### **Emanuelly Noleto Martins**

Graduanda (Ensino médio)

Instituição de atuação atual: Fundação Oswaldo Cruz Rondônia  
Endereço completo: Rua da Beira, nº. 7671, BR 364, Km 3,5,  
CEP-76812-245 - Porto Velho, RO, Brasil.  
E-mail: martinsemanuellynoleto@gmail.com

### **Antonia Adriana Mesquita Santana**

Mestre

Instituição de atuação atual: Hospital de Campanha de Rondônia

Endereço completo: Rua Joaquim Nabuco, n°. 2718, CEP-76804-074, Porto Velho, RO, Brasil.

E-mail: dannamesquita1@hotmail.com

**Sandra Maria Petillo Cardoso**

Bacharel

Instituição de atuação atual: Hospital de Campanha de Rondônia

Endereço completo: Rua Joaquim Nabuco, n°. 2718, CEP-76804-074, Porto Velho, RO, Brasil.

E-mail: sandrapetillocardoso@hotmail.com

**Fabiana Helen Melo Neres**

Bacharel

Instituição de atuação atual: Hospital de Campanha de Rondônia

Endereço completo: Rua Joaquim Nabuco, n°. 2718, CEP-76804-074, Porto Velho, RO, Brasil.

E-mail: fabianahelen1408@gmail.com

**Juan Miguel Villalobos Salcedo**

Doutorado

Instituição de atuação atual: Fundação Oswaldo Cruz Rondônia

Endereço completo: Rua da Beira, n°. 7671, BR 364, Km 3,5, CEP-76812-245 - Porto Velho, RO, Brasil.

Email: juanitto2001@yahoo.com.br

**Rita de Cássia Pontello Rampazzo**

Doutorado

Instituição de atuação atual: Instituto de Biologia Molecular do Paraná - IBMP

Endereço completo: Rua Professor Algacyr Munhoz Mader, n°. 3775, CEP-81350-010, Curitiba, PR, Brasil.

E-mail: rcprampazzo@gmail.com

**Deusilene Souza Vieira**

Doutorado

Instituição de atuação atual: Fundação Oswaldo Cruz Rondônia

Endereço completo: Rua da Beira, n°. 7671, BR 364, Km 3,5, CEP-76812-245 - Porto Velho, RO, Brasil.

E-mail: deusylenebio@hotmail.com

**ABSTRACT**

COVID-19 may be more severe in elder people and/or people presenting comorbidities, possibly leading to death. Therefore, we analyzed the profile of deaths caused by SARS-CoV-2 in part of the Amazon region, associating them to risk factors. 467 cases of death caused by COVID-19 from October 2020 to July 2021 were analyzed and correlated to age group, gender, comorbidities, and other risk factors, using the Chi-squared Test or Fisher's Exact Test as necessary. Deaths occurred in the age group between 17 and 98 years, with a predominance of men (57.4%) and higher concentration in the period between March and April 2021. Systemic arterial hypertension was the most prevalent disease, followed by smoking, cardiovascular disease, and diabetes mellitus. Smoker men

and obese women (and/or with cardiovascular disease) presented higher chances to die, as well as obese people under 65 years and people over 65 years with cardiovascular disease, smokers, or hypertensive ( $p < 0.05$ ). The description of risk groups contributes for the adoption of strategies directed to the most vulnerable populations, as disease monitoring and an increase in vaccination rate, reducing the probability of overloading Brazil's Unified Health System.

**Keywords:** COVID-19, Lethality, Age, Gender

## RESUMO

A COVID-19 pode ser mais severa em pessoas idosas e/ou pessoas que apresentem comorbidades, possivelmente levando à morte. Portanto, analisamos o perfil das mortes causadas pela SRA-CoV-2 em parte da região amazônica, associando-as a fatores de risco. 467 casos de morte causados pela COVID-19 de outubro de 2020 a julho de 2021 foram analisados e correlacionados à faixa etária, sexo, comorbidades e outros fatores de risco, utilizando o Teste Qui-quadrado ou o Teste Exato de Fisher, conforme necessário. As mortes ocorreram na faixa etária entre 17 e 98 anos, com predominância de homens (57,4%) e maior concentração no período entre março e abril de 2021. A hipertensão arterial sistêmica foi a doença mais prevalente, seguida pelo tabagismo, doenças cardiovasculares e diabetes mellitus. Homens fumantes e mulheres obesas (e/ou com doença cardiovascular) apresentaram maiores chances de morrer, assim como pessoas obesas com menos de 65 anos e pessoas com mais de 65 anos com doença cardiovascular, fumantes ou hipertensas ( $p < 0,05$ ). A descrição dos grupos de risco contribuiu para a adoção de estratégias dirigidas às populações mais vulneráveis, como o monitoramento da doença e o aumento da taxa de vacinação, reduzindo a probabilidade de sobrecarga do Sistema Único de Saúde do Brasil.

**Palavras-chave:** COVID-19, Letalidade, Idade, Gênero

## 1 INTRODUCTION

COVID-19, related to Severe Acute Respiratory Syndrome 2 (SARS-CoV-2), caused more than 190,000,000 confirmed infections and 4,000,000 deaths worldwide<sup>1-3</sup>. Brazil presented more than 19,000,000 cases with about 500,000 deaths and lethality of 2,8% putting pressure on the Brazil's Unified Health System during the infection waves<sup>3</sup>. COVID-19 patients may present light, moderate and severe disease according to signs, symptoms and comorbidities that can lead to death<sup>4</sup>.

SARS-CoV-2 presents high transmissibility which favors the emergence of new variants and it may be related to high rates of mortality, evidencing the importance of viral sequencing<sup>5-7</sup>. The main variants of concern (VOC) are Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) related to increase of cases and a worse evolution of the disease<sup>8-10</sup>. Brazil presents the circulation of all VOCs with prevalence of Gamma in the North region<sup>11,12</sup>.

The worsening of the disease and the associated deaths have been related to many factors such as advanced age, systemic arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, obesity, cardiovascular disease, and smoking, that should be studied to better understand the correlation with evolutive cases and viral dynamic <sup>13-17</sup>.

Rondônia, located in Brazilian North region, in the border with other states of the country (Acre, Mato Grosso, Amazonas) and Bolivia presented rates beyond the regional and national numbers for confirmed cases and deaths <sup>18,19</sup>. Despite the high rates of infected patients and deaths by COVID 19 in the Amazon region, there are not enough studies to evaluate harm and comorbidities that can increase the probability of death <sup>15</sup>. Therefore, the aim was to describe causes and comorbidities associated to death caused by SARS CoV-2.

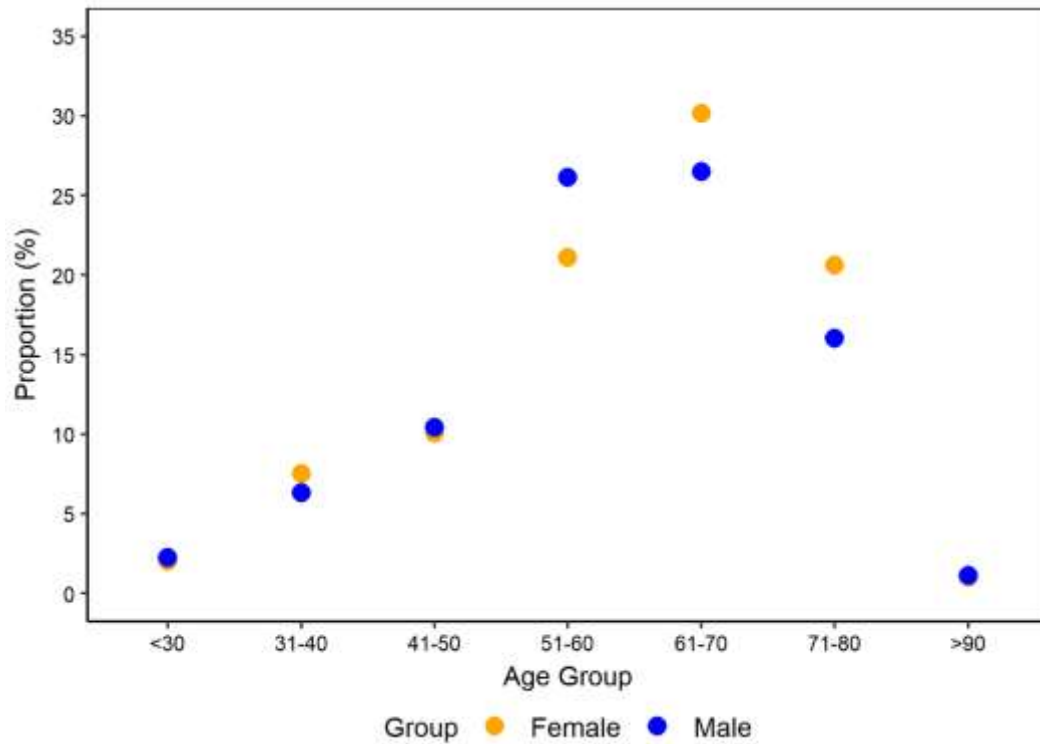
## 2 METHODS

This study was based on a transversal and descriptive cohort composed by 467 cases of death by COVID-19 in Porto Velho, a city of Rondônia State in Brazil, from October 2020 to June 2021. Gender, age group (between 17 and 98 years old), comorbidities and other risk factors were analyzed. The software R (v4.1.0) was used to statistical analysis and graphics construction through Chi-squared Test or Fisher's Exact Test.

## 3 RESULTS

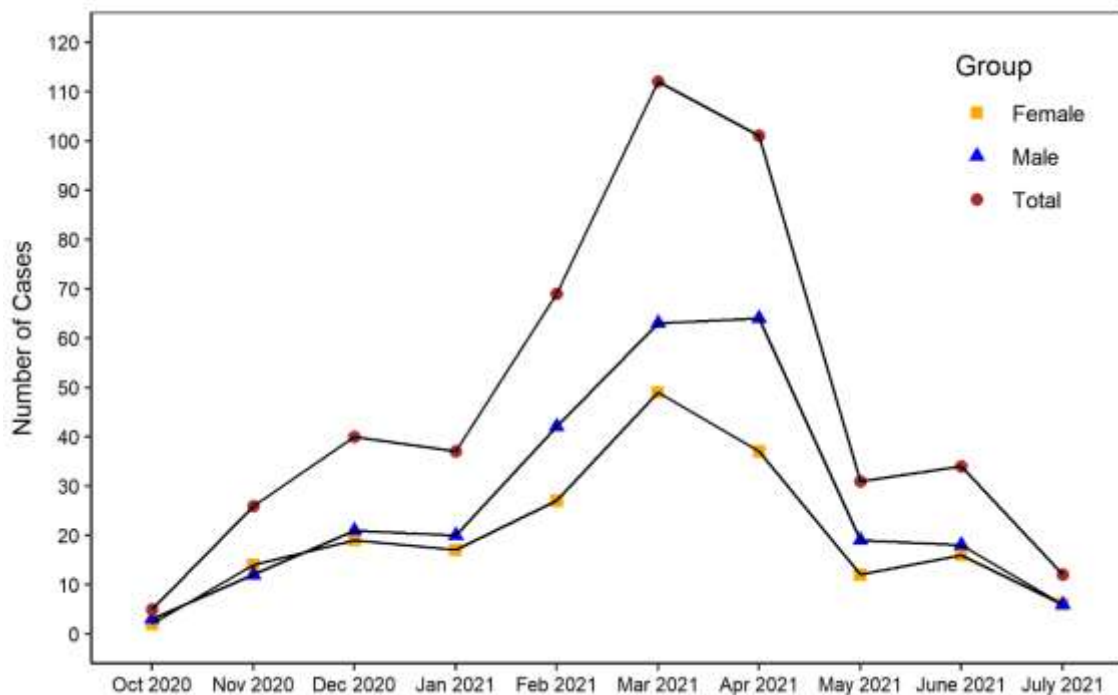
The age group of 467 people in the cohort was between 17 and 98 years with median of 63 years (SD 14.7), being 42,6% (199/467) women and 57,4% (268/467) men. The **figure 1** demonstrates the age profile by gender.

Figure 1. Distribution of age profile by gender of deaths caused by COVID-19.



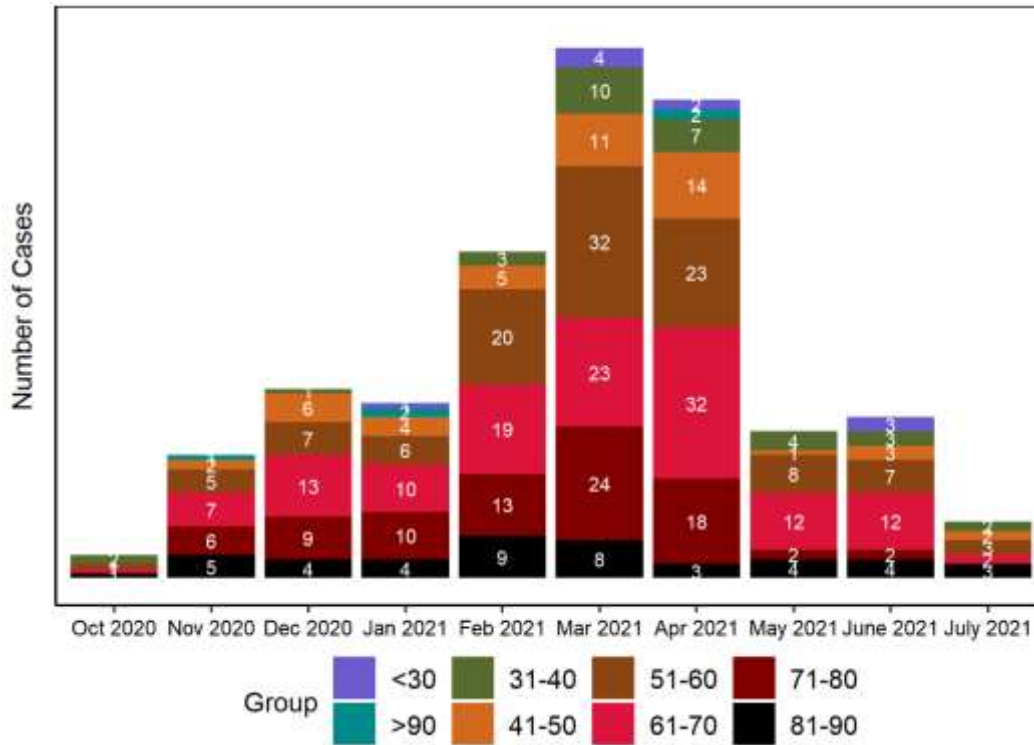
The first death registered happened on October 3<sup>rd</sup> 2020 and the last on July 19<sup>th</sup> 2021. The **figure 2** demonstrates the increasing of deaths since January 2021 with a decrease in April. The index of deaths related to gender was stable from October 2020 to January 2021, with an increase in male deaths from January to April 2021.

Figure 2. Total of deaths by gender along analysed period.



The highest death prevalence was between March and April 2021, being the most affected age groups the ones between 51-60, 61-70 and 71-80 years (**figure 3**). The age groups 51-60 and 61-70 remained the most prevalent in May and June.

Figure 3. Deaths by COVID-19 related to age groups per month of notification.



Systemic arterial hypertension was the most prevalent comorbidities in this study, followed of smoking, cardiovascular disease, and diabetes mellitus (**table 1**).

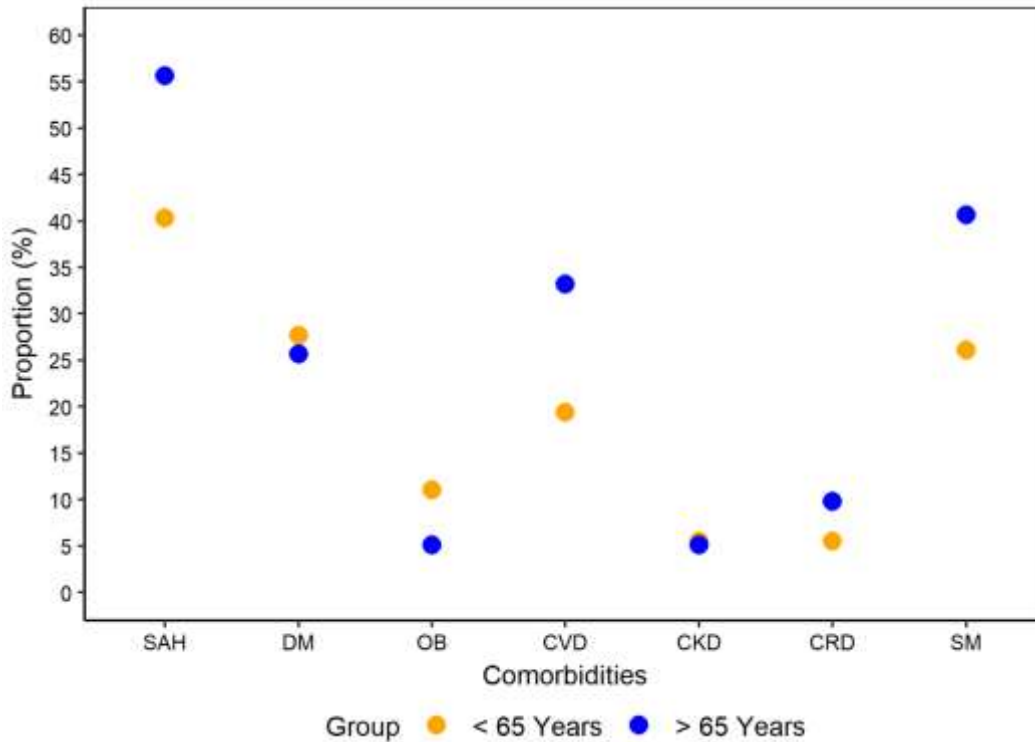
Table 1. Prevalence of comorbidities related to gender in death cases by COVID-19.

	Female (n=199)	Male (n=268)	Total (n=467)	p value	OR (CI 95%)
	% (n)	% (n)	% (n)		
Systemic Arterial Hypertension	52.3 (104)	43.7 (117)	47.3 (221)	0.065	0.708 (0.4814-1.040)
Diabetes Mellitus	21.6 (43)	26.9 (72)	24.6 (115)	0.192	1.332 (0.848-2.101)
Obesity	15.1 (30)	3.4 (9)	8.4 (39)	0.000006*	0.196 (0.071-0.438)
Cardiovascular disease	30.7 (61)	22 (59)	25.7 (120)	0.035*	0.639 (0.412-0.991)
Kidney disease	6.5 (13)	4.5 (12)	5.4 (25)	0.329	0.671 (0.27313-1.636)
Respiratory diseases	6.5 (13)	8.2 (22)	7.5 (35)	0.463	1.279 (0.598-2.841)
Smoking	27.6 (55)	36.6 (98)	32.8 (153)	0.042*	1.508 (0.996-2.297)

\*Significant p value (<0.05)

The comorbidities in death cases by COVID-19 were related to age, been systemic arterial hypertension, obesity, cardiovascular disease, and smoking presenting significant statistical,  $p$  value  $< 0.05$  (figure 4).

Figure 4. Comorbidities related to age group

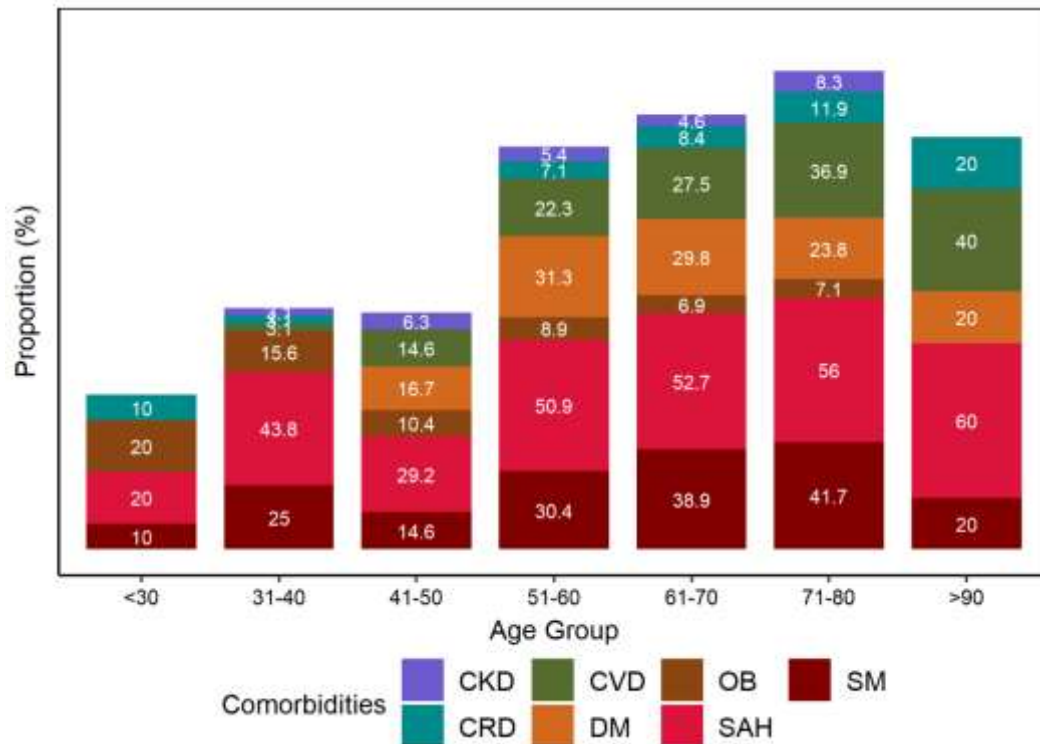


Consideration: People may have more than one disease simultaneously. Legend: SAH = Systemic Arterial Hypertension; DM = Diabetes Mellitus; OB = Obesity; CVD = cardiovascular disease; CKD = chronic kidney disease; CRD = Chronic Respiratory Disease; SM = Smoking.

Cardiovascular diseases, smoking and systemic arterial hypertension in elders over 65 years higher the level to death by COVID-19 with OR of 0.484 (CI 95% = 0.310-0.754,  $p = 0.0006$ ), 0.515 (CI 95% = 0.342-0.776,  $p = 0.0008$ ) and 0.54 (CI 95% = 0.367-0.793,  $p = 0.0009$ ), respectively. The group of SARS-COV2 infected obese individuals under 65 years had a greater chance of dying than others, with OR of 2.292 (CI 95% = 1.073-5.241,  $p = 0.021$ ).

The group of analysis relating comorbidities and different age groups demonstrated that people with hypertension and smokers were prevalent in all age groups (figure 5). Diabetes and cardiovascular diseases carriers had higher proportions from 41 to >90 years and obesity was prevalent among younger individuals, especially <40 years.

Figure 5. Comorbidities related to age group.



Consideration: People may have be more than one disease simultaneously. Legend: SAH = Systemic Arterial Hypertension; DM = Diabetes Mellitus; OB = Obesity; CVD = cardiovascular disease; CKD = chronic kidney disease; CRD = Chronic Respiratory Disease; SM = Smoking.

#### 4 DISCUSSION

SARS-CoV-2 deaths are frequently reported in elderly populations and/or with associated comorbidities<sup>15,20-26</sup>. The epidemiological profiles from European, Asian, and Latin American countries demonstrate that mortality was higher among individuals older than 60 years and males, as in the cohort presented<sup>21-27</sup>.

The temporal distribution of deaths shows that from January 2021 there was a progressive increase in deaths due to COVID-19. These rates followed the increase in lethality rates in the state of Rondônia, recorded in response to the increase in the number of active infections in the same period, known as the second wave<sup>27</sup>. When evaluating the national epidemiological scenario, the Northern region together with the Southeastern region presented the highest mortality rates in Brazil<sup>25-27</sup>.

It is necessary to consider the emergence of the VOC Gamma<sup>19</sup>, proven to be related to cases of reinfection<sup>28</sup> and higher disease severity<sup>29</sup>. The new variant, coming from Amazonas, was associated with the second wave locally in mid-December 2020<sup>11</sup> and a rapid spread in the Northern region<sup>12</sup>. In January 2021, the second wave started in Rondônia probably driven by the same event happened in a border state, the insertion of Gamma variant<sup>12</sup>.



The results showed that, although the death rate is more representative in the elderly population, there is an expressive number of deaths in younger individuals. In Brazil and other countries around the world, lethality rates rise progressively after the age of 50 and peak among individuals older than 60 years<sup>21–23,25–27,30</sup>. It is notable that COVID-19 changed mortality patterns and the presence of comorbidities was an influencer of the early mortality process<sup>15,21–26</sup>.

The influence of comorbidities in the evolution of the disease has been reported since the first infections by SARS-CoV-2, where it was evident that most individuals who progressed to severe complications and death presented secondary pathologies to the viral infection, among them cardiovascular diseases, diabetes mellitus and decompensated respiratory diseases<sup>13,20,31–35</sup>. The correlation of these data presented in the literature and the profile of deaths in the cohort showed that the greatest proportion of the infected carried comorbidities as hypertension, smoking, cardiovascular disease, and diabetes mellitus the most reported conditions, which may have directly influenced the mortality, especially among the youngsters.

Hypertension has already been described as the most frequent disorder in severe cases of COVID-19 and was indicated as a predictor of mortality in several studies performed worldwide<sup>32–34,36</sup>. In Brazil, a multicenter study conducted with 2054 hospitalized individuals described that 52.9% were hypertensive and that the relative risk of dying was higher in this group when compared to others who did not have this comorbidity<sup>37</sup>. In this study, it was observed that 54.7% of deaths were of male, however, among the hypertensive patients, the highest proportion were women.

The second most frequent comorbidity reported was obesity. The relationship between increased body weight and mortality risk has already been investigated, especially among individuals with viral infection by influenza<sup>38</sup>. One of the factors of this relationship is that obese individuals have altered innate and adaptive immune response patterns, characterized by higher concentrations of proinflammatory proteins and lower concentrations of anti-inflammatory proteins<sup>39</sup>.

Obesity and SARS-CoV-2 share common elements of the inflammatory process, which potentializes the viral infection<sup>40</sup>. This mechanism may explain the mortality pattern of the population described in this study, especially among people under 65 years of age, where the highest proportion of obese individuals is concentrated under 40 years of age.

Another relevant observation was the relationship between smoking and evolution to death in individuals older than 65 years. This association has already been investigated and it was evident that infected individuals with a history of smoking presented a higher risk of death <sup>41</sup>. In order to understand this causality, Liu and colleagues (2021) demonstrated that exposure to tobacco and tobacco products significantly increases the expression of ACE2 (described as a cellular receptor for entry of SARS-CoV-2) in various tissues, contributing to the development of COVID-19 and associated complications <sup>42</sup>.

It is important to consider that the period of this study comprised up to July 2021, when the COVID-19 pandemic is in progress with a considerable number of active cases <sup>3</sup> and the insertion of new variants (Gamma and Delta) in Brazil has become a major concern regarding the potential of causing increasing numbers of infections and overloaded health system <sup>7,10,43</sup>.

## 5 CONCLUSION

The description of the death profiles showed that individuals with advanced age and presence of comorbidities represented the largest proportion of deaths. Systemic arterial hypertension, smoking, cardiovascular diseases, and diabetes mellitus were the most frequent pathologies in the cohort and were associated with mortality by COVID-19. Factors associated with an increased risk of death were male smokers and obese women or women with cardiovascular disease, as well as obese people under 65 years, and people over 65 years with cardiovascular disease, smokers, or hypertensive ( $p < 0.05$ ). Deaths occurred considerably in groups comprising economically active individuals, mainly between the age group 51-60 years. This information is important for the identification of risk groups and thus contributes to new strategies for coping with the disease, such as monitoring and vaccinating the most vulnerable populations, decreasing the probability of overburdening the health system.

## ACKNOWLEDGEMENTS

This study was developed by the group of researchers from the Laboratório de Virologia Molecular of the Fundação Oswaldo Cruz Rondônia, but the team of professionals from the Hospital de Campanha de Rondônia was essential to perform in providing the data for this research. The Instituto Nacional de Ciência e Tecnologia de Epidemiologia da Amazônia Ocidental - INCT- EpiAmo has been an important contributor to the scientific development of the Amazon region, as well as the Coordenação de Aperfeiçoamento



Pessoal de Nível Superior - CAPES, which collaborated with financial assistance (scholarships) of some authors.

## REFERENCES

1. Chan JFW, Yuan S, Kok KH, To KKW, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020 Feb;395(10223):514–23.
2. Phan T. Novel coronavirus: From discovery to clinical diagnostics. Vol. 79, *Infection, Genetics and Evolution*. Elsevier B.V.; 2020. p. 104211.
3. Johns Hopkins C-19 M-. COVID-19 Map - Johns Hopkins Coronavirus Resource Center [Internet]. 2021 [cited 2021 Aug 16]. Disponível em: <https://coronavirus.jhu.edu/map.html>
4. Gasmi A, Peana M, Pivina L, Srinath S, Benahmed AG, Semenova Y, et al. Interrelations between COVID-19 and other disorders. *Clin Immunol*. 2021 Mar;224:108651.
5. Banerjee A, Mossman K, Grandvaux N. Molecular Determinants of SARS-CoV-2 Variants. *Trends Microbiol*. 2021 Jul;
6. Botelho-Souza LF, Nogueira-Lima FS, Roca TP, Naveca FG, de Oliveria dos Santos A, Maia ACS, et al. SARS-CoV-2 genomic surveillance in Rondônia, Brazilian Western Amazon. *Sci Rep*. 2021 Dec;11(1):3770.
7. Pascarella S, Ciccozzi M, Zella D, Bianchi M, Benedetti F, Benvenuto D, et al. SARS-CoV-2 B.1.617 Indian variants: Are electrostatic potential changes responsible for a higher transmission rate? *J Med Virol*. 2021 Jul 27;
8. WHO. SARS-CoV-2 Variant Classifications and Definitions [Internet]. 2021 [cited 2021 Aug 16]. Disponível em: <https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html>
9. CDC. Tracking SARS-CoV-2 variants [Internet]. 2021 [cited 2021 Aug 16]. Disponível em: <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>
10. Liu Y, Rocklöv J. The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. *J Travel Med*. 2021 Aug 9;
11. Naveca F, Nascimento V, Souza V, Corado A, Nascimento F, Silva G, et al. COVID-19 epidemic in the Brazilian state of Amazonas was driven by long-term persistence of endemic SARS-CoV-2 lineages and the recent emergence of the new Variant of Concern P.1. *Nat Portf*. 2021;
12. Rede Genômica FIOCRUZ. Variantes de preocupação (VOCs) e de interesse (VOIs) – Genomahcov – Fiocruz [Internet]. 2021 [cited 2021 Aug 12]. Disponível em: <http://www.genomahcov.fiocruz.br/variantes-de-preocupacao-vocs-e-de-interesse-vois/>
13. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020 Feb 15;395(10223):497–506.
14. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of

critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020 May;8(5):475–81.

15. Escobar AL, Rodriguez TDM, Monteiro JC. Lethality and characteristics of deaths due to COVID-19 in Rondônia: an observational study. *Epidemiol e Serviços Saúde.* 2020 Dec;30(1):e2020763.

16. Singh MK, Mobeen A, Chandra A, Joshi S, Ramachandran S. A meta-analysis of comorbidities in COVID-19: Which diseases increase the susceptibility of SARS-CoV-2 infection? *Comput Biol Med.* 2021 Mar;130.

17. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity is associated with higher in-hospital mortality in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism.* 2020 Jul;108.

18. IBGE. Rondônia | Cidades e Estados | IBGE. 2021.

19. Fujino T, Nomoto H, Kutsuna S, Ujiie M, Suzuki T, Sato R, et al. Novel SARS-CoV-2 variant in travelers from Brazil to Japan. *Emerg Infect Dis.* 2021 Apr;27(4):1243–5.

20. Maciel EL, Jabor P, Goncalves E, Tristão-Sá R, Lima R de CD, Reis-Santos B, et al. Factors associated with COVID-19 hospital deaths in Espírito Santo, Brazil, 2020. *Epidemiol e Serviços Saúde.* 2020 Sep;29(4):e2020413.

21. O'Driscoll M, Santos GR Dos, Wang L, Cummings DAT, Azman AS, Paireau J, et al. Age-specific mortality and immunity patterns of SARS-CoV-2. *Nat* 2020 5907844. 2020 Nov;590(7844):140–5.

22. Pastor-Barriuso R, Pérez-Gómez B, Hernán MA, Pérez-Olmeda M, Yotti R, Oteo-Iglesias J, et al. Infection fatality risk for SARS-CoV-2 in community dwelling population of Spain: nationwide seroepidemiological study. *BMJ.* 2020 Nov;371.

23. Undurraga EA, Chowell G, Mizumoto K. COVID-19 case fatality risk by age and gender in a high testing setting in Latin America: Chile, March–August 2020. *Infect Dis Poverty* 2021 10(1):1–11. 2021 Feb;10(1):1–11.

24. Bello-Chavolla OY, González-Díaz A, Antonio-Villa NE, Fermín-Martínez CA, Márquez-Salinas A, Vargas-Vázquez A, et al. Unequal Impact of Structural Health Determinants and Comorbidity on COVID-19 Severity and Lethality in Older Mexican Adults: Considerations Beyond Chronological Aging. *Journals Gerontol Ser A.* 2021 Feb;76(3):e52–9.

25. Silva GA e, Jardim BC, Lotufo PA. Mortalidade por COVID-19 padronizada por idade nas capitais das diferentes regiões do Brasil. *Cad Saude Publica.* 2021;37(6).

26. Sanchez M, Moura E, Moreira J, Lima R, Barreto I, Pereira C, et al. Mortality from COVID-19 in Brazil: analysis of death's civil registry from 2020 January to 2021 February TT - Mortalidade por COVID-19 no Brasil: uma análise do Registro Civil de óbitos de janeiro de 2020 a fevereiro de 2021 [Internet]. 2021. Disponível em: [file:///scielo.php?script=sci\\_arttext&pid=https://preprints.scielo.org/index.php/scielo/preprint/view/2012&lang=pt](file:///scielo.php?script=sci_arttext&pid=https://preprints.scielo.org/index.php/scielo/preprint/view/2012&lang=pt)

27. Brazil. Boletim Epidemiológico Especial: Doença pelo Coronavírus – COVID-19. Brasília, DF; 2021.
28. Naveca F, Costa C da, Nascimento V, Souza V, Corado A, Nascimento F, et al. SARS-CoV-2 reinfection by the new Variant of Concern (VOC) P.1 in Amazonas, Brazil. *virological.org*, 2021. 2021.
29. Faria NR, Claro IM, Candido D, Franco LAM, Andrade PS, Coletti TM, et al. Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings. *virological.org*. 2021.
30. Porto EF, Domingues AL, Souza AC de, Miranda MKV, Froes MB da C, Pasqualinoto SRV. Mortalidade por Covid-19 no Brasil: perfil sociodemográfico das primeiras semanas. *Res Soc Dev*. 2021 Jan;10(1):e34210111588.
31. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA*. 2020 Mar;323(11):1061.
32. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020 Mar 26;368.
33. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. 2020 May 1;94.
34. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020 Mar 28;395(10229):1054–62.
35. Cecconi M, Piovani D, Brunetta E, Aghemo A, Greco M, Ciccarelli M, et al. Early Predictors of Clinical Deterioration in a Cohort of 239 Patients Hospitalized for Covid-19 Infection in Lombardy, Italy. *J Clin Med* 2020, Vol 9, Page 1548. 2020 May 20;9(5):1548.
36. Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020 May;55(5):2000547.
37. Marcolino MS, Ziegelmann PK, Souza-Silva MVR, Nascimento IJB, Oliveira LM, Monteiro LS, et al. Clinical characteristics and outcomes of patients hospitalized with COVID-19 in Brazil: Results from the Brazilian COVID-19 registry. *Int J Infect Dis*. 2021 Jun 1;107:300–10.
38. Luzi L, Radaelli MG. Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. *Acta Diabetol*. 2020 Jun 1;57(6):1.
39. Andersen CJ, Murphy KE, Fernandez ML. Impact of Obesity and Metabolic Syndrome on Immunity. *Adv Nutr*. 2016;7(1):66.
40. Michalakis K, Ilias I. SARS-CoV-2 infection and obesity: Common inflammatory

and metabolic aspects. *Diabetes Metab Syndr Clin Res Rev.* 2020 Jul 1;14(4):469–71.

41. Nassar Y, Mokhtar A, Elhadidy A, Elsayed M, Mostafa F, Rady A, et al. Outcomes and risk factors for death in patients with coronavirus disease-2019 (COVID-19) pneumonia admitted to the intensive care units of an Egyptian University Hospital. A retrospective cohort study. *J Infect Public Health.* 2021 Jun;

42. Liu H, Xin J, Cai S, Jiang X. Mendelian randomization analysis provides causality of smoking on the expression of ACE2, a putative SARS-CoV-2 receptor. *Elife.* 2021 Jul 6;10.

43. Shah SA, Moore E, Robertson C, McMenamin J, Katikireddi SV, Simpson CR, et al. Predicted COVID-19 positive cases, hospitalisations, and deaths associated with the Delta variant of concern, June–July, 2021. *Lancet Digit Heal.* 2021 Aug;