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ORIGINAL ARTICLE

Epidemiological survey on the benefit of neuraminidase inhibitors on severe acute respiratory syndrome due to COVID-19

Levantamento epidemiológico do benefício de inibidores de neuraminidase na síndrome respiratória aguda grave por COVID-19

Encuesta epidemiológica del beneficio de inhibidores de neuraminidase en síndrome respiratorio agudo severo por COVID-19

Thamara Graziela Flores[1] ORCID 0000-0002-2748-1612

Carlos Fernando Antunes Gonçalves[1] ORCID 0000-0002-3734-4304

Isis Niero Volpato[1] ORCID 0000-0002-7852-7342

Fernanda Barbisan[1] ORCID 0000-0002-2960-7047

Melissa Agostini Lampert[1] ORCID 0000-0002-3708-8400

Ivana Beatrice Manica da Cruz[1] ORCID 0000-0003-3008-6899

Nathália Cardoso de Afonso Bonotto[1] ORCID 0000-0003-3733-3549

[1]Universidade Federal de Santa Maria, Santa Maria, RS, Brasil.

E-mail: prpgp@ufsm.br

Address: Avenida Roraima, 1000, Cidade Universitária, Santa Maria, RS, Brasil.

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ABSTRACT

Background and objectives: The COVID-19 pandemic and its consequent severe acute respiratory syndrome (SARS) have taken the lives of millions since 2020. The use of neuraminidase inhibitors is a promising alternative in treating this disease, with several studies on off-label use being conducted since the beginning of the pandemic, but none of them have a large sample size and analyze multiple risk factors. The purpose of this article is to identify possible associations between various factors and risk of hospitalization, need for ventilation and death, as well as the influence of the prescription of Zanamivir and Oseltamivir on these same indicators. **Methods**: In this transversal study, approximately 900,000 medical records from all regions of Brazil were collected from the Ministry of Health database, and after that, proper statistical analysis of the variables was performed. **Results:** Hospitalization was associated with gender, ethnicity, education, local urbanization, State, and its percentage of elderly, as well as the climate.

The prescription of Zanamivir and Oseltamivir was associated with higher incidence of symptoms, lower hospitalization and death rate, and lower need for invasive and non-invasive ventilation. Medical records from146,160 patients were excluded due to SARS not caused by COVID-19. **Conclusion:** From this data, it is possible to draw a risk profile for hospitalization by SARS and consider the use of Zanamivir and Oseltamivir as a treatment for these patients.
Keywords: *SARS. Zanamivir. Oseltamivir. Covid-19.*

RESUMO

Justificativa e objetivos: A pandemia de COVID-19 e sua consequente síndrome respiratória aguda grave (SRAG) levaram milhões de pessoas a óbito desde 2020. O uso de inibidores da neuraminidase é uma alternativa promissora no tratamento dessa doença, com vários estudos sobre o uso *off-label* sendo conduzidos desde o início da pandemia, mas nenhum que tenha um grande tamanho amostral e que analise vários fatores de risco. O objetivo deste artigo é identificar possíveis associações entre diversos fatores e risco de hospitalização, necessidade de ventilação e óbito, assim como a influência da prescrição de Zanamivir e Oseltamivir nos mesmos indicadores. **Métodos:** Neste estudo transversal, foi feito o levantamento de aproximadamente 900 mil prontuários de todas as regiões do Brasil, provenientes de dados do Ministério da Saúde, e em seguida foi realizado o tratamento estatístico adequado das variáveis. **Resultados:** A hospitalização foi associada a sexo, etnia, escolaridade, urbanização do local, Estado e porcentagem de idosos do mesmo, assim como o clima. Já a prescrição de Zanamivir e Oseltamivir foi associada a maior incidência de sintomas, menor taxa de hospitalização e óbito e menor necessidade de ventilação invasiva e não-invasiva. Foram excluídos 146.160 prontuários devido a SRAG não ocasionada pela COVID-19. **Conclusão:** Com esses dados, é possível traçar um perfil de risco para hospitalização por SRAG e considerar o uso de Zanamivir e Oseltamivir como tratamento para esses pacientes.
Descritores: *SRAG. Zanamivir. Oseltamivir. Covid-19.*

RESUMEN

Justificación y objetivos: la pandemia Covid-19 y su consiguiente síndrome respiratorio agudo severo (SRAS) han muerto millones de personas desde 2020. El uso de inhibidores de la neuraminidasa es una alternativa prometedora en el tratamiento de esta enfermedad, con varios estudios sobre el uso *off-label* que se realiza desde el principio de la pandemia, pero ninguno que tenga un tamaño de muestra grande y analice múltiples factores de riesgo. El propósito de este artículo es identificar posibles asociaciones entre varios factores y el riesgo de hospitalización, necesidad de ventilación y muerte, así como la influencia de la prescripción de Zanamivir y Oseltamivir en los mismos indicadores. **Métodos:** En este estudio transversal, se encuestaron a los datos del Ministerio de Salud de aproximadamente 900,000 registros de todas las regiones de Brasil, después de que se realizó un tratamiento estadístico adecuado de las variables. **Resultados**: La hospitalización se asoció con género, etnia, educación, urbanización del sitio, Estado y porcentaje de ancianos, así como el clima. La prescripción de zanamivir y oseltamivir se asoció con la mayor incidencia de síntomas, menor hospitalización y tasa de mortalidad y menor necesidad de ventilación invasiva y no invasiva. Se excluyeron 146,160 registros médicos debido a SRAS no causado por Covid-19. **Conclusión:** con estos datos, es posible dibujar un perfil de riesgo para la hospitalización por SRAS y considerar el uso de zanamivir y oseltamivir como tratamiento para estos pacientes.
Palabras clave: *SRAS. Zanamivir. Oseltamivir. Covid-19.*

INTRODUCTION

By mid-2016, the *Coronavirus* family of viruses had caused two pandemics that, despite the higher case fatality rate, did not present such a high transmissibility.[1] In 2019, a new viral pathology originating in Wuhan, China, which is caused by a new virus of the *Coronavirus* family, SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), COVID-19, has caused more than 6 million deaths worldwide, with excess mortality — more than the expected deaths from all causes — estimated at 18 million.[2,3]

Its most severe symptom, the severe acute respiratory syndrome (SARS), is defined as bilateral pulmonary infiltrates and hypoxemia without evidence of cardiogenic pulmonary edema, commonly leading to death. SARS consists of inflammation-mediated pulmonary changes, such as increased permeability of the alveolar-capillary membrane, pulmonary edema with consequent reduction in pulmonary compliance, and changes in the ventilation/perfusion ratio.[4-8]

The clinical management of SARS consists of several pharmacological and non-pharmacological alternatives with the objective of containing viral proliferation and its consequent inflammatory response.[9] One of the alternatives are anti-influenza drugs, which act by inhibiting the viral enzyme neuraminidase, such as zanamivir and oseltamivir.

In this sense, it is observed that many patients were submitted to the use of neuraminidase inhibitors because these were already prescribed for the treatment of common influenza, since it is also viral-caused.[10] *In vitro* and *in vivo* studies suggest that the antiviral effect of these drugs is not directly on the virus, but rather by modulating the immune system, especially neutrophils, to fight the viral infection.[11,12] Because this class of drugs inhibits the active site of neuraminidase, which is similar to that of the S1 spike protein of SARS-CoV-2, it possibly offers similar pharmacological benefits. However, the impact of the use of these drugs on SARS mortality and its relationship with the etiologic agent needs more clinical evidence.

METHODS

In this observational and retrospective study, data was gathered from secondary sources from the Ministry of Health. The variables analyzed were: hospitalizations for

SARS regardless of cause, use of neuraminidase inhibitors, age, sex, length of stay, need for intubation, hospitalization in intensive care unit and mortality.[13]

The total study population was 1,048,575 individuals who entered Brazil's public health system due to COVID-19 symptoms. This system collected medical records from all parts of the country, removed the identification of patients and made the compilation of data publicly accessible in a *Microsoft Excel* spreadsheet. Because the records were filled during the peak of COVID-19, some data was considered "ignored" in the database, thus being excluded from the sample. In addition to the ignored data, individuals with SARS that was not caused by COVID-19 or whose tests were inconclusive were also excluded, totaling 146,160 exclusions.

Statistical tests for association were used (χ^2 univariate analysis or Fisher's exact test), the correlation was performed by Spearman's correlation coefficient with Bonferroni correction to analyze the association of deaths with the use of neuraminidase inhibitors. The *Statistical Package for the Social Sciences* - SPSS (version 21) software was used for all statistical analyses. The data reported in this article is publicly available without personal identifiers.

RESULTS

In the period analyzed, it was identified that 1,048,575 individuals entered the database of the Ministry of Health due to SARS symptoms; of these, 146,160 were listed as ignored and were excluded from the analyses. The classification of SARS is shown in Table 1.

Table 1. Classification of SARS cases (Brazil, 2021, n=902,415)

Etiological cause	**N**	**%**
Influenza	740	0.1
Unknown Etiological agent	1,715	0.2
Other respiratory viruses	5,461	0.6
Unspecified	146,574	16.2
COVID-19	747,925	82.9
Total	902,415	100

It was observed that 82.9% (n=747,925) of SARS cases were due to SARS-CoV-2, the etiologic agent of COVID-19, and that the other causes added together were

responsible for the remaining 16.9% (n=154,490) of hospitalizations. The profile of hospitalizations by SARS classification is shown in Table 2.

Table 2. SRAG profile (Brazil, 2021, n=902,415)

		Agente etiológico									
		Influenza		**Other respiratory viruses**		**Unknown etiologic agent**		**Unspecified**		**COVID-19**	
		n	%	n	%	n	%	n	%	N	%
Sex	Female	328	44.3	2,465	45,1	789	46.0	70,459	48.1	332,807	44.5
	Male	412	55.7	2,995	54,8	926	54.0	76,065	51.9	415,014	55.5
Ethnic group	White	264	40.2	2,156	51,0	843	53.2	55,738	46.1	333,985	53.8
	Black	28	4.3	190	4,5	107	6.7	7,520	6.2	30,357	4.9
	Yellow	9	1.4	12	0,3	22	1.4	1,243	1.0	6,719	1.1
	Brown	355	54.1	1,855	43,9	608	38.3	56,046	46.4	248,307	40.0
	Indigenous	0	0.0	17	0,4	6	0.4	323	0.3	1,002	0.2
Schooling	Illiterate	14	6.1	524	15.6	121	13.5	6,908	12.8	15,302	5.7
	Elementary school	61	26.5	140	4.2	243	27.1	13,845	25.7	70,098	26.1
	Middle school	33	14.3	58	1.7	230	25.7	7,869	14.6	50,572	18.9
	High school	57	24.8	55	1.6	145	16.2	9,716	18.0	88,827	33.1
	College	20	8.7	24	0.7	57	6.4	3,139	5.8	40,420	15.1
	Not applicable	45	19.6	2,553	76.1	100	11.2	12,460	23.1	3,056	1.1
Zone	Urban	585	92.9	4,479	94.1	1,398	91.2	12,2138	93.7	620,649	94.4
	Rural	44	7.0	110	2.3	131	8.5	7,253	5.6	34,266	5.2

	Suburban	1	0.2	172	3.6	4	0.3	942	0.7	2,216	0.3

When analyzing table 2, it was observed that male sex was predominant in all types of SARS, the same occurring with the ethnicity that was predominantly white. The occurrence of SARS stratified by schooling was variable, where in SARS due to influenza (26.5%), in unknown etiological agent (27.1%) and not specific (25.7%), individuals with elementary education between 1st and 5th grade were predominant, while in SARS by other etiological agents there was a higher occurrence in individuals where schooling is not applied, such as immigrants or indigenous people, and in SARS due to COVID-19, the predominant level of schooling was high school (33.1%). The predominant place of residence in all types of SARS was urban.

The State that had the most SARS cases was São Paulo (21.1 %), followed by Minas Gerais (11.7%), Rio de Janeiro (7.4%) and Paraná (7.3%). The distribution of cases by region was as follows: Southeast (48.8%), Northeast (20.6%), South (17.7%), Midwest (9%) and North (6.5%).

In the population analyzed, 4.3% (n=29,845) of the individuals were prescribed neuraminidase inhibitors, whose prescription profile is shown in table 3.

Table 3. Profile of the use of neuraminidase inhibitors (Brazil, 2021, n=902,415)

		Prescription of neuraminidase inhibitors			
		Yes		**No**	
		N	%	n	%
Sex	Female	13,553	45.4%	300,561	45.1%
	Male	16,288	54.6%	366,248	54.9%
Ethnicity	White	13,681	52.2%	307,012	53.6%
	Black	1,388	5.3%	29,057	5.1%
	Yellow	264	1.0%	5,839	1.0%
	Brown	10,803	41.2%	229,914	40.1%
	Indigenous	57	0.2%	947	0.2%
Schooling	Illiterate	1,069	7.4%	19,680	7.1%
	Elementary school	3,583	24.8%	72,566	26.0%
	Middle school	2,314	16.0%	50,525	18.1%
	High school	3,853	26.7%	84,643	30.3%
	College	1,575	10.9%	35,387	12.7%
	Not applicable	2,032	14.1%	16,288	5.8%

Zone	Urban	25,173	92.5%	574,465	94.1%
	Rural	1,875	6.9%	33,502	5.5%
	Suburban	173	0.6%	2,635	0.4%

The mean age of individuals who used neuraminidase inhibitors was 50.08 years (± 24.52) and of those who did not use was 54.31 years (±20.55).

The prescription of neuraminidase inhibitors was associated with ethnicity ($p<0.001$), schooling ($p<0.001$) and zone of residence ($p<0.001$), with no association with gender.

The presentation of symptoms in individuals who were prescribed neuraminidase inhibitors was significantly different when compared to those who did not have the prescription, as can be analyzed in Table 4.

Table 4. Comparison of symptoms versus antiviral use (Brazil, 2021, n=902,415)

		Notification form variable ANTIVIRAL USE				
		Yes		No		
		N	%	n	%	p-value
Fever	Yes	17,847	68.0%	365,576	62.7%	*<0.001*
	No	8,393	32.0%	217,026	37.3%	
Cough	Yes	22,473	83.2%	456,561	75.9%	
	No	4,548	16.8%	144,645	24.1%	
Sore throat	Yes	6,046	27.3%	115,251	22.6%	
	No	16,132	72.7%	395,714	77.4%	
Dyspnea	Yes	22,348	82.5%	482,746	79.3%	
	No	4,754	17.5%	126,109	20.7%	
Respiratory distress	Yes	19,685	76.2%	397,027	69.1%	
	No	6,140	23.8%	177,562	30.9%	
Saturation	Yes	20,570	78.5%	456,771	76.7%	
	No	5,626	21.5%	139,101	23.3%	
Diarrhea	Yes	4,653	21.2%	91,985	18.1%	
	No	17,328	78.8%	416,184	81.9%	
Abdominal pain	Yes	2,159	10.2%	45,253	9.2%	
	No	18,905	89.8%	445,781	90.8%	
Fatigue	Yes	9,335	41.6%	187,251	36.4%	
	No	13,124	58.4%	32,7624	63.6%	
Loss of smell	Yes	3,392	16.0%	63,732	12.9%	
	No	17,765	84.0%	429,877	87.1%	

Loss of taste	Yes	3,518	16.7%	64,880	13.2%
	No	17,598	83.3%	428,137	86.8%
Vomiting	Yes	3,130	14.4%	61,783	12.3%
	No	18,544	85.6%	439,330	87.7%

Individuals who were prescribed neuraminidase inhibitors were more likely to have fever (1.250; CI: 1.229 to 1.296), cough (1.539; CI 1.491 to 1.588), sore throat (1.273;CI: 1236 to 1.310), dyspnea (1.218 CI: 1.181 to 1.256), respiratory distress (1.413; CI: 1.374 to 1.454), changes in O_2 saturation (1.109: CI;1.077 to 1.141), diarrhea (1.205;CI: 1.167 to 1.243), abdominal pain (1.119:CI; 1.072 to 1.169), fatigue (1.233;CI: 1.201 to 1.265), loss of smell (1.273; CI: 1.229 to 1.320), loss of taste (1.303; CI: 1.258 to 1.350) and vomiting (1.191: CI; 1.191 to 1.147).

The fact that the symptoms were more prevalent did not translate into a higher rate of hospitalization in the intensive care unit (ICU) or use of ventilatory support, with 30.2% (n=7,783) of the individuals who used neuraminidase inhibitors being admitted to the ICU against 30.8% (n=189,485) of those who did not. In fact, there is an inverse association of the use of neuraminidase inhibitors and ICU admission, with a higher risk for individuals who were not prescribed (1.001; CI 1.000 to 1.002, *p=0.023*).

Regarding the use of ventilation, individuals who used neuraminidase inhibitors had a higher percentage of noninvasive ventilation use (63.7%), followed by no use of ventilatory support (18.4%) and only 17.9% (n=4,650) used invasive ventilation. Those who did not use neuraminidase inhibitors had similar rates, with 63.4% (n=378,369) using noninvasive ventilation, 20.0% (n=123,179) not using ventilatory support and 18.7% (115,071) using invasive ventilation. There was an inverse association between the use of neuraminidase inhibitors and ventilatory support ($p<0.001$). Non-prescription of neuraminidase inhibitors increased the chance of using invasive mechanical ventilation by 1.159 (CI: 1.056 to 1.273).

Death occurred in 34.3% (n=174,028) of the cases. Of these, 3.9% (n=6,701) had been prescribed neuraminidase inhibitors and 96.1% (n=167,327) had no prescription. The use of neuraminidase inhibitors was associated with a higher chance of cure ($p<0.001$), increasing it by 1.055 times (CI: 1.045 to 1.065).

There was no difference between the classes of neuraminidase inhibitors ($p=0.076$).

In predicting cure, the antiviral drug Oseltamivir had prediction, with significance of p=0.027 and Exp(β) of 1.095 (CI: 1.010 to 1.187).

DISCUSSION

The use of neuraminidase inhibitors was associated with a higher incidence of symptoms, probably as a result of the greater severity of the patients' clinical case with prescription indication. Some studies indicate that although there is a positive association between the use of neuraminidase inhibitors and increased symptoms, the risk of admission to the ICU was higher for patients who did not use these drugs.[11] As large-scale ICU admission overwhelms the health system, the adoption of neuraminidase inhibitors for symptomatic patients becomes a very relevant public health tool.

In cases of hospitalization, the need for invasive mechanical ventilation was lower in patients who used neuraminidase inhibitors. The data reinforces the suggestion that these drugs be used in large scale in the healthcare system. In addition, the death rate was lower in patients who had a prescription. Thus, the results suggest the indication of neuraminidase inhibitors prescription as a treatment for SARS complications, increasing the chance of cure. Other studies suggest a positive correlation between the use of neuraminidase inhibitors before treatment and shorter hospital stays, which also avoids the situation of lack of ICU beds.[14]

With the arrival of COVID-19 in Brazil, there was an increase in cases of hospitalization for SARS, a result observed in our etiological analysis. When analyzing the causes of hospitalization for SARS, the main cause identified was the SARS-CoV-2 virus.[2,15]

When analyzing the epidemiological characteristics, such as gender, we observed that male sex had a predominance in SARS cases regardless of the etiological agent. This finding converges with those found in other studies already carried out, which indicate greater susceptibility to infections and higher mortality associated with this disease in males.[16,17]

Another finding is the predominance of white ethnicity in SARS-CoV-2 SARS cases. This phenomenon is possibly a result of greater access to laboratory tests by this ethnic group, with underreporting occurring in the others as a result of non-testing, and the situation as a whole is a consequence of social inequalities.[18,19]

The data also showed an association between schooling and hospitalization for SARS. It is noticed that cases of SARS by SARS-CoV-2 are more frequent in people with

complete high school education, while cases of contagion by influenza, unknown and non-specific etiological agent are more frequent in the population niche of elementary education between 1st and 5th grade. This data suggests that SARS-CoV-2 has a tendency to infect individuals with a higher level of education compared to other etiologic agents, but the possibility of underreporting makes it impossible to be sure of this conclusion. As education level is associated with socioeconomic status, and SARS-CoV-2 possibly had its initial spread by means of tourist transport, such as planes and ships, these restricted to individuals with higher purchasing power, the association between cases and level of education is possibly another reflection of social inequalities.[20]

In addition, there was a relationship with zone of residence. The results indicate a higher incidence of SARS of all etiological agents in urban areas. This data can be justified by the fact that these regions have a higher rate of contagion due to the difficulty of maintaining social distancing and the fact that the majority of the Brazilian population lives in urban areas, as indicated by the latest data from IBGE (The Brazilian Statistics Bureau).[21]

It is noticed that the most populous states such as São Paulo, Minas Gerais and Rio de Janeiro reported higher numbers of SARS cases, and this results from several factors, such as the proportional relationship between population density and contagion, as evidenced in other studies, and also the late adoption of social distancing by some States, notably Rio de Janeiro.[15,22]

Finalizing the relationships between SARS and demographics, a relationship was observed between hospitalizations and percentage of elderly people in the States. The data shows that in the southern States, which have a higher proportion of elderly population, SARS rates are higher, which confirms previous knowledge of other studies that indicate higher rates of complications of the disease in the elderly.[21,23]

Another factor that explains the relationship between the proportion of elderly and hospitalization for SARS is the climate. The southern region of the country has a subtropical climate, which increases the rate of contagion.

Regarding the prescription of neuraminidase inhibitors, white patients had proportionally more prescription of neuraminidase inhibitors in relation to other ethnicities, possibly because the latter had on average better economic condition and access to healthcare, as well as higher rates of testing and drug prescription.[18]

The prescription of neuraminidase inhibitors was associated with lower schooling. This data may be due to the prophylactic measures instituted by the Ministry of Health,

which mostly covers public hospitals, where the profile of the average patient is less educated compared to private hospitals, which have a larger structure and more effective medications. On the other hand, there are studies that demonstrate lower morbidity and mortality in populations with higher educational level in Brazil and the USA.[24]

The limitations of this study are related to data collection since there is no system of digital medical records in the Brazilian public health system and this fact limits the scope of the data. We can also affirm that there is a limitation associated with filling out the forms, a fact that culminated in the exclusion of medical records.

With the data presented, a patient profile more conducive to hospitalization, need for invasive or non-invasive ventilation and death from SARS can be visualized. This profile can be used as a basis for the preparation of screening protocols in health units, as well as updating treatment guidelines for patients with SARS in their various presentations.[25] An association can also be observed between prescription of Zanamivir and Oseltamivir and lower rates of hospitalization and death, as well as less need for invasive and non-invasive ventilation, suggesting the use of these neuraminidase inhibitors as a treatment for patients at risk as well as a public health tool to reduce the rate of bed occupancy in the healthcare system.

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REFERENCES

1. Rabaan AA, Al-Ahmed SH, Haque S, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview. Infez Med. 2020;28(2):174–84.
2. Platto S, Wang Y, Zhou J, et al. History of the COVID-19 pandemic: Origin, explosion, worldwide spreading. Biochem Biophys Res Commun. 2021;538:14–23. http://dx.doi.org/10.1016/j.bbrc.2020.10.087
3. COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. Lancet Lond Engl. 2022;399(10334):1513–36. http://dx.doi.org/10.1016/S0140-6736(21)02796-3
4. Diamond M, Peniston HL, Sanghavi D, et al. Acute Respiratory Distress Syndrome. Em: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 http://www.ncbi.nlm.nih.gov/books/NBK436002/
5. Wiener-Kronish JP, Albertine KH, Matthay MA. Differential responses of the endothelial and epithelial barriers of the lung in sheep to Escherichia coli endotoxin. J Clin Invest. 1991;88(3):864–75. http://dx.doi.org/10.1172/JCI115388

6. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med. 2001;163(6):1376–83. http://dx.doi.org/10.1164/ajrccm.163.6.2004035
7. Gattinoni L, Pesenti A. The concept of "baby lung". Intensive Care Med. 2005;31(6):776–84. http://dx.doi.org/10.1007/s00134-005-2627-z
8. Dantzker DR, Brook CJ, Dehart P, et al. Ventilation-perfusion distributions in the adult respiratory distress syndrome. Am Rev Respir Dis. 1979;120(5):1039–52. http://dx.doi.org/10.1164/arrd.1979.120.5.1039
9. Cascella M, Rajnik M, Aleem A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19). Em: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022 http://www.ncbi.nlm.nih.gov/books/NBK554776/
10. Liu, J., Zhang, S., Wu, Z. et al. Clinical outcomes of COVID-19 in Wuhan, China: a large cohort study. Ann. Intensive Care 10, 99 (2020). https://doi.org/10.1186/s13613-020-00706-3
11. Tan Q, Duan L, Ma Y, et al. Is oseltamivir suitable for fighting against COVID-19: In silico assessment, in vitro and retrospective study. Bioorg Chem. 2020;104:104257. https://dx.doi.org/10.1016/j.bioorg.2020.104257
12. de Oliveira Formiga R, Amaral FC, Souza CF, et al. Neuraminidase is a host-directed approach to regulate neutrophil responses in sepsis and COVID-19 [published online ahead of print, 2022 Dec 16]. Br J Pharmacol. 2022;10.1111/bph.16013. https://dx.doi.org/10.1111/bph.16013
13. Ministério da Saúde (BR). OpenDataSUS: SRAG 2021 a 2023 [Internet]. Brasília: Ministério da Saúde; [atualizado em 2023 mar 2; citado em 2023 mar 2]. Disponível em: https://opendatasus.saude.gov.br/dataset/srag-2021-a-2023
14. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med. 2020;383(19):1813–26. http://dx.doi.org/10.1056/NEJMoa2007764
15. Niquini RP, Lana RM, Pacheco AG, et al. SRAG por COVID-19 no Brasil: descrição e comparação de características demográficas e comorbidades com SRAG por influenza e com a população geral. Cad Saúde Pública. 2020;36(7):e00149420. http://dx.doi.org/10.1590/0102-311x00149420
16. Pradhan A, Olsson PE. Sex differences in severity and mortality from COVID-19: are males more vulnerable? Biol Sex Differ. 2020;11:53. http://dx.doi.org/10.1186/s13293-020-00330-7
17. Prinelli F, Trevisan C, Noale M, et al. Sex- and gender-related differences linked to SARS-CoV-2 infection among the participants in the web-based EPICOVID19 survey: the hormonal hypothesis. Maturitas. 2022;158:61–9. http://dx.doi.org/10.1016/j.maturitas.2021.11.015
18. Retrato das Desigualdades de Gênero e Raça - Ipea https://www.ipea.gov.br/retrato/indicadores_pobreza_distribuicao_desigualdade_renda.html
19. Whittaker C, Walker PGT, Alhaffar M, et al. Under-reporting of deaths limits our understanding of true burden of covid-19. BMJ. 2021;375:n2239. http://dx.doi.org/10.1136/bmj.n2239
20. Aikens N, Barbarin O. Socioeconomic Differences in Reading Trajectories: The Contribution of Family, Neighborhood, and School Contexts. J Educ Psychol. 2008;100:235–51. http://dx.doi.org/10.1037/0022-0663.100.2.235

21. Estimativas da população residente para os municípios e para as unidades da federação | IBGE https://www.ibge.gov.br/estatisticas/sociais/populacao/9103-estimativas-de-populacao.html?=&t=resultados
22. Teller J. Urban density and Covid-19: towards an adaptive approach. Build Cities. 2021;2(1):150–65. http://dx.doi.org/10.5334/bc.89
23. Pirâmides Etárias e Envelhecimento da População - Atlas Socioeconômico do Rio Grande do Sul https://atlassocioeconomico.rs.gov.br/piramides-etarias-e-envelhecimento-da-populacao
24. Maciel EL, Jabor P, Goncalves Júnior E, et al. Fatores associados ao óbito hospitalar por COVID-19 no Espírito Santo, 2020. Epidemiol E Serviços Saúde. 2020 http://scielo.iec.gov.br/scielo.php?script=sci_abstract&pid=S1679-49742020000400026&lng=pt&nrm=iso&tlng=pt http://dx.doi.org/10.1590/s1679-49742020000400022
25. Cartilha do Uso Racional do medicamento fosfato de oseltamivir e zanamivir para os casos de infecção pelo vírus da Influenza — Português (Brasil) https://www.gov.br/saude/pt-br/composicao/sctie/daf/publicacoes/2022/2022-0015-cartilha-uso-racional-de-medicamento-fosfato-de-oseltamivir-e-zanamivir.pdf/view

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Carlos Fernando Antunes Gonçalves and **Isis Niero Volpato** contributed to the design, analysis and writing of the article;

Thamara Graziela Flores contributed to the conception, planning, design, writing, review and final approval of the article;

Fernanda Barbisan, Ivana Beatrice Manica da Cruz and **Melissa Agostini Lampert** contributed to the conception, planning and design of the article.

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