The increase in the risk of severity and fatality rate of covid-19 in southern Brazil after the emergence of the Variant of Concern (VOC) SARS-CoV-2 P.1 was greater among young adults without pre-existing risk conditions

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ABSTRACT

Background

The SARS-CoV-2 P.1 variant has been considered as “variant of concern (VOC)” since the end of 2020 when it was firstly identified in the Brazilian state of Amazonas and from there spread to other regions of Brazil. This variant was associated with an increase in transmissibility and worsening of the epidemiological situation in the places where it was detected. The aim of this study was to analyze the severity profile of covid-19 cases in the Rio Grande do Sul state, southern region of Brazil, before and after the emergence of the P.1 variant, considering also the context of the hospitals overload and the collapse of health services.

Methods

We analyzed data from the Influenza Epidemiological Surveillance Information System, SIVEP-Gripe (Sistema de Informação de Vigilância Epidemiológica da Gripe) and compare two epidemiological periods: the “first wave” comprised by cases occurred during November and December 2020 (EW 45 to 53) and the “second wave” with cases occurred in February 2021 (EW 5 to 8), considering that in this month there was a predominance of the new variant P.1. We calculated the proportion of severe forms among the total cases of covid-19, the case fatality rates (CFR) and hospital case fatality rate (hCFR) over both waves time set using the date of onset of symptoms as a reference. We analyzed separately the patients without pre-existing conditions of risk, by age and sex. For comparison between periods, we calculated the Risk Ratio (RR) with their respective 95% confidence intervals and the p-values.

Findings

We observed that in the second wave there were an increase in the proportion of severe cases and covid-19 deaths among younger age groups and patients without pre-existing conditions of risk. The proportion of people under the age of 60 among the cases that evolved to death raised from 18% (670 deaths) in November and December (1st wave) to 28% (1370 deaths) in February (2nd wave). A higher proportion of patients without pre-existing risk conditions was also observed among those who evolved to death due to covid-19 in the second wave (22%, 1,077 deaths) than in the first one (13%, 489 deaths). The CFR for covid-19 increased overall and in different age groups, in both sexes. The increase occurred in a greatest intensity in the population between 20 and 59 years old and among patients without pre-existing risk conditions. Female 20 to 39 years old, with no pre-existing risk conditions, were at risk of death 5.65 times higher in February (95%CI = 2.9 - 11.03; p <0.0001) and in the age group of 40 and 59 years old, this risk was 7.7 times higher (95%CI = 5.01-11.83; p <0.0001) comparing with November-December.

Interpretation

Our findings showed an increase in the proportion of young people and people without previous illnesses among severe cases and deaths in the state of RS after the identification of the local transmission of variant P.1 in the state. There was also an increase in the proportion of severe cases and in the CFR, in almost all subgroups analyzed, this increase was heterogeneous in different age groups and sex. As far as we know, these are the first evidences that the P.1 variant can disproportionately increase the risk of severity and deaths among population without pre-existing diseases, suggesting related changes in pathogenicity and virulence profiles. New studies still need to be done to confirm and deepen these findings.

Introduction

Since the beginning of 2021, international authorities have shown great concern with the P.1 variant of SARS-CoV-2, also known as 20J / 501Y.V3 or Variant of Concern 202101/02 (VOC-202101/02). This variant probably emerged between late November and early December 2020 in Amazonas, northern Brazil, with rapid dissemination to other regions and other countries[1]. The introduction of this variant was temporally associated with increased transmissibility of covid-19 causing a critical epidemiological scenario in different places where it was detected as the Amazonas, in the north region, and the Paraná and the Rio Grande do Sul (RS) states, in the south of the country[2–5]. In the Amazonas state, a collapse of the health system was observed, which made it difficult to assess the real impact of the P.1 variant on the lethality by covid-19, which may have increased due to the overload of the health system and not exclusively by the intrinsic characteristics of the variant[2]. The emergence of variant P.1 in the RS state was confirmed by the virus identification from a patient with no travel history and presenting symptoms beginning on January 29 (EW 4/2021)[6]. In the following weeks there was a sudden increase in cases of covid-19 in several regions of the state, simultaneously. Virological surveillance data showed that in February, the variant P.1 corresponded to about 70% of the viruses sequenced in the RS state. [5,7]
The exponential increase in the hospitalization rate observed in the RS state could be explained, on one hand, by the P.1 circulation as this variant has being 2.6 times more transmissible (95% Confidence Interval (CI): 2.4–2.8) than the previous one [8]. However, on other hand, studies have suggested that the P.1 variant can also lead to more severe conditions, which would increase the need for hospitalization and contribute to the increase observed in hospitalization rates. In order to provide more evidences related to the change in the hospitalization and deaths patterns among covid-19 cases in the RS state, we performed an epidemiological analysis describing and comparing the severity and mortality profile of covid-19 cases in the RS state, considering two periods before and after the emergence of variant P.1.

Methodology

An observational, retrospective epidemiological study of covid-19 cases reported in the National Influenza Epidemiological Surveillance Information System (SIVEP-Gripe) of the Ministry of Health of Brazil was performed.

Database and setting

The Rio Grande do Sul state has 11,422,973 inhabitants, it is the 5th largest state in population size in the country, corresponding to 5.4% of the Brazilian population. Life expectancy at birth is 78.0 years and the HDI is 0.787[9]. The Unified Health System (SUS), the public health system in Brazil, is responsible for 72% of the 3,411 ICU beds available in the state[7].
The notification of suspected and confirmed cases of covid-19 is mandatory in Brazil, both in public and private health services. Suspected cases of covid-19 can be confirmed by laboratory, clinical, clinical-epidemiological or clinical-radiological criteria, according to the Brazilian guidelines (supplements) that follow the recommendations of the World Health Organization. In the SIVEP-Gripe system, cases can be classified as influenza syndrome (influenza-like illness (ILI)) and severe cases (severe acute respiratory infections (SARI)). SARI cases are confirmed cases of covid-19 requiring hospitalization associated with any of

the following signs and symptoms: dyspnea, difficulty breathing, O2 saturation below 95% in ambient air or cyanosis. In children, in addition to the previous items, the following nasal wing beats, intercostal circulation, dehydration and lack of appetite are included.
We accessed information on demographic data, self-reported ethnicity, presence of pre-existing risk conditions (supplements), data on the onset of symptoms, hospitalization and hospital outcome, as well as data on the occupation of ward beds and intensive care unit (ICU) beds. The data were made available by the Secretariat of Health of the Rio Grande do Sul state and by the Ministry of Health of Brazil through open access online platforms with anonymous data. The period of analysis was from the epidemiological week 17/2020 (started on April 19th 2020) to the epidemiological week 11/2021 (ended on March 20th 2021). The data were exported for analysis on April 2nd 2021. [7,10]

Data analysis

We defined two epidemiological periods for the analysis: the “first wave” comprised by cases occurred during November and December 2020 (EW 45 to 53) and the “second wave” with cases occurred in February 2021 (EW 5 to 8), considering that in this month there was a predominance of the new variant P.1. The month of March 2021 was not included in the second wave due to the fact that, at the beginning of this month, the health system reached 100% of the occupancy of ICU beds, which may affect the risk of death.
We calculated the proportion of severe forms among the total cases of covid-19, the case fatality rates (CFR) and hospital case fatality rate (hCFR) over both waves time set using the date of onset of symptoms as a reference. The hCFR was calculated dividing the number of deaths by the total number of patients who had already been classified by hospital discharged or death[11].
We calculated the proportion of severe forms (SARI) between the total number of covid-19 cases and the case fatality rate (CFR), in the first and second waves. We analyzed separately the patients without pre-existing conditions of risk, by age and sex. For comparison between these periods, we calculated the Risk Ratio (RR) with their respective 95% confidence intervals and the p-values.
Additionally, the bed occupancy rate in the ICU was used as an indicator of the capacity of the local health system because it is the level of assistance required for the life risk patients management and it was considered by the health sector in the RS state as the principal indicator to signalize the exhaustion of the hospital capacity during the pandemic.
The data were analyzed using the STATA 16 software and followed the recommendations of the **RE**porting of studies **C**onducted using **O**bservational **R**outinely-collected **D**ata (**RECORD**) guidelines[12], attached checklist. This study did not require approval from any research ethics committee as all data were anonymous and obtained from open and public open source databases.

Results

In the state of Rio Grande do Sul, 230,986 cases of covid-19 were confirmed in the first wave and 150,942 cases in the second wave, while the number of severe cases was 11,951 and 13,128, respectively (table 1). Mortality was also higher in the second wave (4,859 deaths) when compared to the first wave (3,809 deaths). The proportion of cases of covid-19 by age group did not change between the first and second waves, however, the proportion of people

under 60 years of age among severe cases increased from 39% in the first wave to 47 %, in the second wave. Also, the proportion of people under the age of 60 among the cases that evolved to death raised from 18% (670 deaths) in November and December (1st wave) to 28% (1370 deaths) in February (2nd wave) (data summarized from the Table 1).

There was no change in the proportion of women among severe covid-19 cases or among deaths between the two analyzed periods and the same profile was observed in the proportion of covid-19 cases without pre-existing risk conditions keeping around 87% in the two waves (87%). However, the proportion of patients without pre-existing risk conditions among severe cases was higher in the second wave (33%, 4,324 severe cases) than in the first wave (25%, 3,021 severe cases) (Table 1). A higher proportion of patients without pre-existing risk conditions was also observed among those who evolved to death due to covid-19 in the second wave (22%, 1,077 deaths) than in the first one (13%, 489 deaths) (Table 1).

After the emergence of the variant P.1 (week 4/2021) in the RS state a rapid increase in the incidence of covid-19 was observed (Figure 1). The proportion of patients with severe forms of covid-19 in the first wave was 5% and after the introduction of the P.1 variant this value almost doubled, quickly reaching values close to 10% between EW 6 and 9. The increase in the total number of covid-19 cases associated with an increase in the proportion of severe cases led to an abrupt increase in the number of patients admitted from the second half of February (Figure 1).

From the end of January, an increasing tendency in the hCFR overlaps with the begging of the local transmission of the P.1 variant. This increase occurred 2 weeks before the increase in the number of hospitalized patients and preceded by 4 weeks the exhaustion of the ICU beds, which occurred from March 3 (Figure 2).

The case fatality rate also has increased in all age groups after the identification of the local transmission of the variant P.1 (figure 3). The age groups of 20 to 39 years old and of 40 to 59 years old presented a higher proportional increase in the second wave than in the first one (figure 3). The increase in the CFR begins to be noticed as of EW 4, that is, 6 weeks before the exhaustion of ICU vacancies in the state.

With the exception of the group of people under 20 years old, a general increase in the proportion of severe cases in different age groups and sex was observed (table 2). However, this increase was prominent in the population between 20 and 59 years old and among patients without pre-existing risk conditions. The proportion of severe cases raised in the second wave in both sexes [female RR= 1.7 (95% CI = 1.64 -1.76; p <0.0001); male RR= 1.66 (1.61 - 1.72; p <0.0001)] (Table 2).The increase in the proportion of severe cases was greater in the 20- to 39-year-old group and in both sex than in the other age groups [female RR = 2.24 (95% CI = 1.99 - 2.52; p <0.0001); male RR = 2.56 (95% CI = 2.31 - 2.84; p <0.0001)].

The proportion of severe cases more than doubled among a population with no pre-existing diseases from the first to the second wave in both sexes (Table 2). In the age group between 20 and 39 years old, the increase in the proportion of severe cases was greater than in the other age groups [(Female RR = 2.45 (95% CI = 2.05 - 2.92; p<0.0001; Male RR = 2.64 (2.31 - 3.02; p <0.0001)].

Additionally, the CFR for covid-19 increased overall and in different age groups, in both sexes, when comparing the first and second waves. The increase in CFR occurred in a greatest intensity in the population between 20 and 59 years old and among patients without pre-existing risk conditions(table 2). Women in the 20 to 39 age group, with no pre-existing risk conditions, were at risk of death 5.65 times higher in February (95%CI = 2.9 - 11.03; p

<0.0001) and in the age group of 40 and 59 years old, this risk was 7.7 times higher (95%CI = 5.01-11.83; p <0.0001).
The same profile was observed among men without previous diseases: the CFR was 5.9 (95%CI = 3.2 - 10.85; p <0.0001) higher in the second wave among adults between 20 and 39 years old and 4.86 higher (95%CI = 3.73 -6.33; p <0.0001) in February among men between 40 and 59 years old.
Among the population under 20 years of age, the CFR did not change, except for the female group. In this group, there was a significant increase (RR = 11.3 (1.42-90.55); p <0.01). However, this result should be analyzed with caution due to the large wide confidence interval and the small number of events in this age group.

Discussion

Our results show that there was a general increase in the severity of cases and in the CFR for covid-19 in RS state after confirmation of the community transmission of variant P.1, and that this increase started before the overload of the health system and it was higher among young people without previous diseases. There was an increase in the proportion of patients under 60 years of age and of patients without pre-existing risk conditions between severe cases and deaths.
The increase in the proportion of hospitalized cases among cases of covid-19 in 2021 reversed a downward trend in the proportion of hospitalized patients that had occurred since the beginning of the pandemic, this fact preceded the increase in the total number of hospitalized patients. Thus, the increase in severity contributed to the overload of the local health system leading to the filling of the ICU beds. As we do not yet have specific treatment for covid-19 in the initial phase of the disease to prevent worsening, this increase in the proportion of severe cases cannot be attributed to problems in health care system. The fact that the increase in CFR and hCFR occurred simultaneously with the confirmation of the emergence of variant P.1 in the state and preceded by several weeks the overload of the health system reinforces the hypothesis that the risk of death among covid-19 patients increased regardless of overload of the hospital care system.
Although there was no shortage of beds in the wards during any analyzed period of the pandemic, a proportion of the cases with symptoms that started in late February may have had difficulty in hospitalization in the ICU in March and this may have contributed to the greatest increase in CFR and in hCFR. However, this does not explain why the difference was more striking in the population of young adults, without previous diseases, than between the elderly and the population in general. Vaccination also does not seem to be a plausible explanation for the risk changes between the age groups and in the population with pre-existing diseases, since at the end of February the vaccine was only being applied to health professionals, institutionalized elderly and over 80 years old. In this age group, until February 28, 48% (156,440 individuals) had recently received the first dose and only 0.7% (2,307 individuals) had received the second dose of the covid-19 vaccine (vacina.saude.rs.gov.br).

Comparison with related studies

Our studies reinforce previous findings that indicate that a P.1 variant appears to be more lethal than the previous one, especially among young patients[2,4,13]. In a previous study in Amazonas, we found that in the subgroup of female patients, the difference in risk of death was greater than in the male population, in the present study we found similar results[2].

Studies in the United Kingdom found an increase in CFR in patients with a confirmed diagnosis of variant B.1.1.7 compared to the risk ratio of previous strains 1.64 (95% confidence interval 1.32 to 2.04)[14] and 1.61 (1.42-1.82) [15].
The increase in risk of death among variant B.1.1.7 patients in the United Kingdom calculated from dividing the CFR among B.1.1.7 patients by the CFR among non-B.1.1.7 patients was relatively homogeneous in the different age groups and in both the sexes. In females, it ranged from 1.46 in those over 85 years old to 1.59 in those under 35 years old. In males, it ranged from 1.47 in those over 85 years old to 1.55 in 35-54 years old[15].
Our study revealed a great variability in RR among the different groups by sex, age group and presence of pre-existing conditions. The heterogeneity observed between the age groups was greater when we analyzed the subgroup of the population without preexisting risk conditions where we found that the CFR in the female sex in the second wave was 1.95 times (95CI = 1.38-2.76) the CFR of the first wave in the population over 85 years old and was 7.7 times (95% CI = 5.01-11.83; p <0.0001) in the population between 40 and 59 years old. In the male population without previous diseases, the CFR in the second wave was 2.18 (95% CI 1.62-2.93) times the CFR of the first wave in the population over 85 years old and 5.9 (95% CI 3 , 2-10,85; p <0, 0001) higher in the range between 20 and 39 years old. This heterogeneity occurs not only in the RR of the CFR, but also in the increase in the proportions of severe forms (RR of Severity, table 2), which excludes the impact of the overload of the health system, as we mentioned above.

Implications of our findings

Brazil has one of the worst epidemiological situations for covid-19 in the world, both in the number of cases and in the number of deaths and their rates.[13] The situation has worsened greatly since the emergence of the P.1 variant, first in the Amazon region and then throughout the country. The presence of a large proportion of patients already infected in that region may have contributed to the selection of a strain with an immune escape capacity[16]. This phenomenon may also explain the emergence of a more transmissible strain, but not a more lethal one. A year has passed since the beginning of the SARS-CoV-2 pandemic and a major change in the epidemiological scenario appears to be the emergence of these new variants.
Previous studies already exist that the P.1 variant is more transmissible and has the capacity to escape immunological.[3,8] The present study suggests that this variant leads to more severe and lethal results than previous strains. In addition, this variant was able to increase severity in specific groups that were previously more spared (women, youth and patients without pre-existing risk conditions). This set of characteristics should be an alert and reinforce the importance of better understanding the epidemiological, virological, pathophysiological, immunological and clinical aspects associated with this and other variants, therefore, an international effort must be organized to increase this knowledge.

Strengths and limitations

One of the strengths of our study is its size, which includes all cases of covid-19 from the RS state officially reported to the Ministry of Health during a period when the P.1 variant was introduced in the state. Another strength is the fact that it is studying a period in which there was not yet a complete depletion of health resources in the studied place.
This study has some limitations, such as the use of secondary data, which can present problems in the quality, integrity and delays in the recorded data. Patients were not tested

individually to see if it was a strain of SARS-CoV-2, for comparison of groups. We assume that as of February, the proportion of variant P.1 among patients with covid-19 was higher than in November and December, although it is quite likely, considering other studies in reference units in the state, this assumption is quite inaccurate.
The use of CFR and hCFR as severity indicators based on epidemiological surveillance data can lead to different types of bias, however, it remains a useful tool, especially in emergency situations in public health.[17–20]
This is an initial analysis in which a limited number of available variables have been assessed and additional individual risk factors have not been explored in depth. Despite these limitations, the results obtained in this study suggest a temporal association between the emergence of variant P.1 and severity indicators related to covid-19 measured by CFR and hCFR, in addition to a potential causal association between exposure to the new variant of SARS -CoV-2 (P.1). Therefore, subsequent specific studies must be carried out to evaluate these hypotheses.

Conclusions

Our findings showed an increase in the proportion of young people and people without previous illnesses among severe cases and deaths in the state of RS after the identification of the local transmission of variant P.1 in the state. There was also an increase in the proportion of severe cases and in the CFR, in almost all subgroups analyzed, this increase was heterogeneous in different age groups and sex. As far as we know, these are the first evidences that the P.1 variant can disproportionately increase the risk of severity and deaths among population without pre-existing diseases, suggesting related changes in pathogenicity and virulence profiles. New studies still need to be done to confirm and deepen these findings.

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Statement of conflict of interest

The authors declare that this is a study carried out on the initiative of the researchers themselves, and does not represent the opinion of the institutions to which they are affiliated. The authors declare no conflict of interest.

Contributions of authors

André Ricardo Ribas Freitas: conceptualisation, data curation, formal analysis, investigation, methodology, project administration, validation, visualisation, writing original draft, and writing review & editing.
Daniele Rocha Queiróz Lemos: writing original draft, writing – review & editing
Otto Albuquerque Beckedorff: data curation, have accessed verified the underlying data, writing – review & editing.
Luciano Pamplona de Góes Cavalcanti: writing – review & editing
Andre M Siqueira: writing – review & editing
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Eliana Nogueira Castro de Barros: writing original draft, writing – review & editing

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Table 1: Demographic, underlying conditions and diagnostic criteria of cases, severe cases and deaths due to covid-19 during the first (Nov-Dec/2020 and second waves (Feb/2021) in the Rio Grande do Sul state, Brazil.

	Covid-19 (all cases)				Severe				Deaths			
	Nov-Dec/2020		Feb/2021		Nov-Dec/2020		Feb/2021		Nov-Dec/2020		Feb/2021	
N	230996		150952		11961		13138		3809		4859	
Age group												
0-19 ys	20548	9%	14545	10%	116	1%	88	1%	4	0%	10	0%
20-39 ys	96716	42%	61910	41%	1038	9%	1615	12%	100	3%	241	5%
40 - 59 ys	75456	33%	49107	33%	3449	29%	4473	34%	566	15%	1119	23%
60 - 79 ys	33092	14%	22114	15%	5395	45%	5454	42%	2017	53%	2496	51%
80 and more ys	5184	2%	3276	2%	1963	16%	1508	11%	1122	29%	993	20%
Sex												
Female	124882	54%	80912	54%	5414	45%	5955	45%	1699	45%	2267	47%
Ethnicity												
White	166105	72%	110900	73%	8835	74%	9116	69%	1754	46%	1960	40%
Mixed ethnicity	8100	4%	6125	4%	396	3%	343	3%	86	2%	80	2%
Black	7857	3%	4860	3%	410	3%	367	3%	76	2%	82	2%
Asian	1553	1%	408	0%	21	0%	24	0%	5	0%	2	0%
Indigenous	321	0%	95	0%	31	0%	14	0%	6	0%	2	0%
N. D.	47050	20%	28554	19%	2258	19%	3264	25%	1882	49%	2733	56%
Diagnostic criteria												
RT-PCR	146808	64%	82043	54%	9809	82%	9221	70%	3339	88%	3595	74%
Immunochromatographic test	75806	33%	65666	44%	1354	11%	3167	24%	329	9%	1081	22%
Another test	5960	3%	1954	1%	133	1%	121	1%	34	1%	31	1%
Clinical criteria	1430	1%	682	0%	51	0%	127	1%	1	0%	11	0%
Clinical and image criteria	640	0%	444	0%	581	5%	444	3%	97	3%	133	3%
Clinical-epidemiological criteria	339	0%	132	0%	20	0%	27	0%	8	0%	5	0%
N. D.	3	0%	21	0%	3	0%	21	0%	1	0%	3	0%
Underlying conditions												
No	201320	87%	130612	87%	3021	25%	4324	33%	489	13%	1077	22%

Table 2: Cases, severe cases and deaths due to covid-19 and case fatality rate (CFR) during first (Nov-Dec/2020 and second waves (Feb/2021) by sex, age group and absence of underlying conditions in the Rio Grande do Sul state, Brazil..

	November-December					February					Risk ratio (Feb/Nov-Dec)			
Female	**Covid-19**	**Severe**	**Deaths**	**Severity (%)**	**CFR**	**Covid-19**	**Severe**	**Deaths**	**Severity (%)**	**CFR**	**Severity (%)**	**p**	**CFR**	**p**
0-19 ys	10811	60	1	0.6%	0.01%	7635	48	8	0.6%	0.10%	1.13(0.78-1.65)	0.5195	11.33(1.42-90.55)	<0.01
20 - 39 ys	52879	466	45	0.9%	0.09%	33226	657	106	2.0%	0.32%	2.24(1.99-2.52)	<0.0001	3.75(2.65-5.31)	<0.0001
40 - 59 ys	40481	1399	223	3.5%	0.55%	26259	1823	476	6.9%	1.81%	2.01(1.88-2.15)	<0.0001	3.29(2.81-3.85)	<0.0001
60 - 79 ys	17616	2420	880	13.7%	5.00%	11786	2586	1139	21.9%	9.66%	1.6(1.52-1.68)	<0.0001	1.93(1.78-2.11)	<0.0001
80 and more	3095	1069	550	34.5%	17.77%	2006	841	538	41.9%	26.82%	1.21(1.13-1.3)	<0.0001	1.51(1.36-1.68)	<0.0001
All ages	124882	5414	1699	4.3%	1.36%	80912	5955	2267	7.4%	2.80%	1.7(1.64-1.76)	<0.0001	2.06(1.94-2.19)	<0.0001
female/total (%)	54%	45%	45%			54%	45%	47%						
Male														
0-19 ys	9737	56	3	0.6%	0.03%	6910	40	2	0.6%	0.03%	1.01(0.67-1.51)	0.9705	0.94(0.16-5.62)	0.9676
20 - 39 ys	43837	572	55	1.3%	0.13%	28684	958	135	3.3%	0.47%	2.56(2.31-2.84)	<0.0001	3.75(2.74-5.13)	<0.0001
40 - 59 ys	34975	2050	343	5.9%	0.98%	22848	2650	643	11.6%	2.81%	1.98(1.87-2.09)	<0.0001	2.87(2.52-3.27)	<0.0001
60 - 79 ys	15476	2975	1137	19.2%	7.35%	10328	2868	1357	27.8%	13.14%	1.44(1.38-1.51)	<0.0001	1.79(1.66-1.93)	<0.0001
80 and more	2089	894	572	42.8%	27.38%	1270	667	455	52.5%	35.83%	1.23(1.14-1.32)	<0.0001	1.31(1.18-1.45)	<0.0001
All ages	106114	6547	2110	6.2%	1.99%	70040	7183	2592	10.3%	3.70%	1.66(1.61-1.72)	<0.0001	1.86(1.76-1.97)	<0.0001
Total	230996	11961	3809			150952	13138	4859						
Whithout underlying conditions														
Female	**Covid-19**	**Severe**	**Deaths**	**Severity (%)**	**CFR**	**Covid-19**	**Severe**	**Deaths**	**Severity (%)**	**CFR**	**Severity (%)**	**p**	**CFR**	**p**
0-19 ys	10316	31	0	0.3%	0.00%	7272	17	0	0.2%	0.00%	0.78(0.43-1.4)	0.4109	-	
20 - 39 ys	49236	200	11	0.4%	0.02%	30887	307	39	1.0%	0.13%	2.45(2.05-2.92)	<0.0001	5.65(2.9-11.03)	<0.0001
40 - 59 ys	34689	442	25	1.3%	0.07%	22341	649	124	2.9%	0.56%	2.28(2.02-2.57)	<0.0001	7.7(5.01-11.83)	<0.0001
60 - 79 ys	12149	370	99	3.0%	0.81%	7893	557	201	7.1%	2.55%	2.32(2.04-2.63)	<0.0001	3.13(2.46-3.97)	<0.0001
80 and more	1645	134	55	8.1%	3.34%	1058	119	69	11.2%	6.52%	1.38(1.09-1.75)	<0.05	1.95(1.38-2.76)	<0.0005
All ages	108035	1177	190	1.1%	0.18%	69451	1649	433	2.4%	0.62%	2.18(2.02-2.35)	<0.0001	3.55(2.99-4.2)	<0.0001
female/total (%)	54%	39%	39%			53%	38%	40%						
Male														
0-19 ys	9313	28	0	0.3%	0.00%	6650	21	0	0.3%	0.00%	1.05(0.6-1.85)	0.8605	-	
20 - 39 ys	42028	329	13	0.8%	0.03%	27414	567	50	2.1%	0.18%	2.64(2.31-3.02)	<0.0001	5.9(3.2-10.85)	<0.0001
40 - 59 ys	30429	794	72	2.6%	0.24%	19661	1241	226	6.3%	1.15%	2.42(2.22-2.64)	<0.0001	4.86(3.73-6.33)	<0.0001
60 - 79 ys	10473	564	145	5.4%	1.38%	6812	706	278	10.4%	4.08%	1.92(1.73-2.14)	<0.0001	2.95(2.42-3.59)	<0.0001
80 and more	1042	129	69	12.4%	6.62%	624	140	90	22.4%	14.42%	1.81(1.46-2.25)	<0.0001	2.18(1.62-2.93)	<0.0001
All ages	93285	1844	299	2.0%	0.32%	61161	2675	644	4.4%	1.05%	2.21(2.09-2.35)	<0.0001	3.29(2.87-3.77)	<0.0001
Total	201320	3021	489			130612	4324	1077						

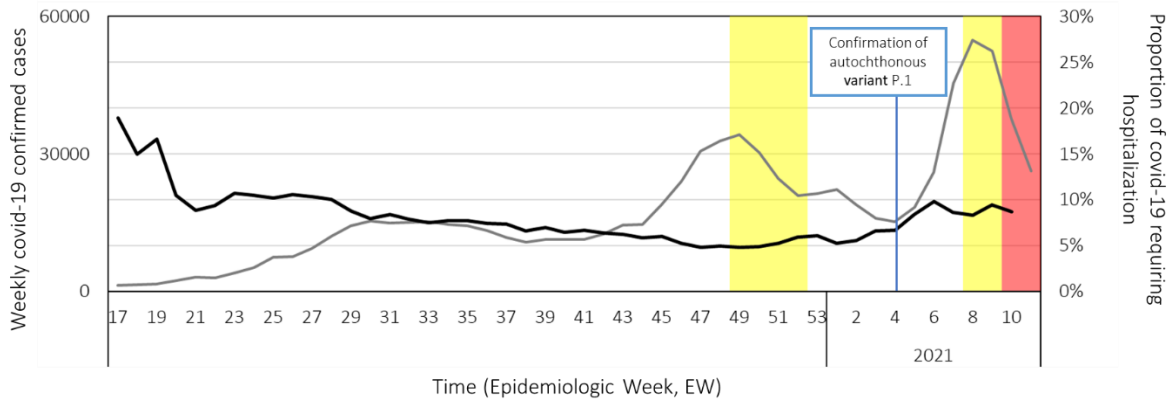

Figure 1: Grey line: number of new covid-19 cases (scale on the left); Black line: proportion of covid-19 cases requiring hospitalization by severe acute respiratory infection (SARI) cases among all covid-19 cases(scale on the rigth). Yellow area: time period when the bed ICU occupancy rate is between 80-100%; Red area: time period when the bed ICU occupancy rate is over 100%.

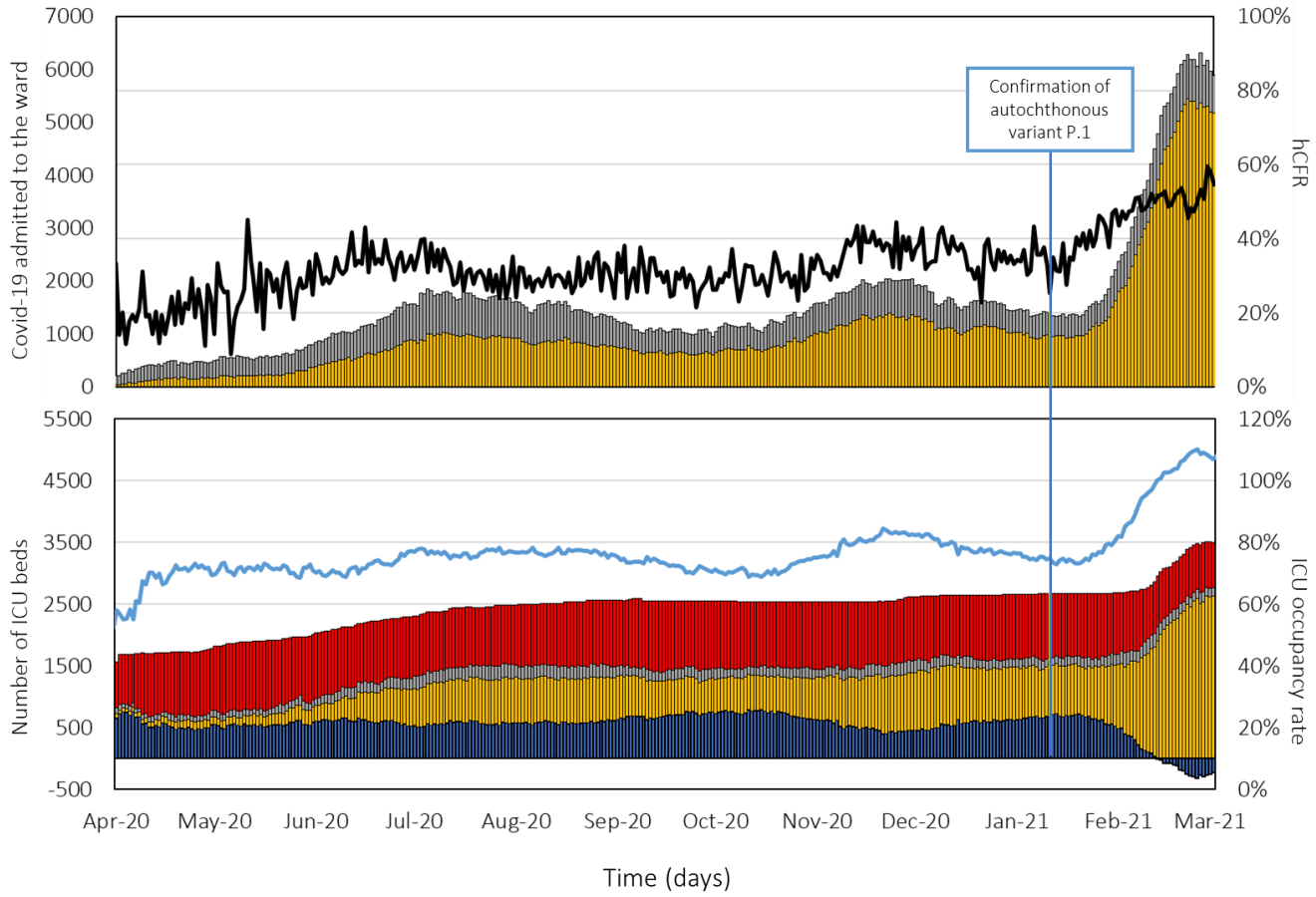

Figure 2: Above: number of beds occupied with covid-19 admitted to the ward (scale on the left) - yellow column confirmed cases, gray columns suspected cases, black line hospital case fatality rate (hCFR, scale on the rigth). Below: number of beds occupied with patients admitted to the ICU (scale on the left), yellow columns of covid-19 confirmed , gray columns suspected of covid-19, red columns other causes de admission, blue columns of beds available (negative numbers indicate that there is more demand than bed available), blue line ICU occupancy rate (scale on the right, values greater than 100% days when the health network had more demand than supply).

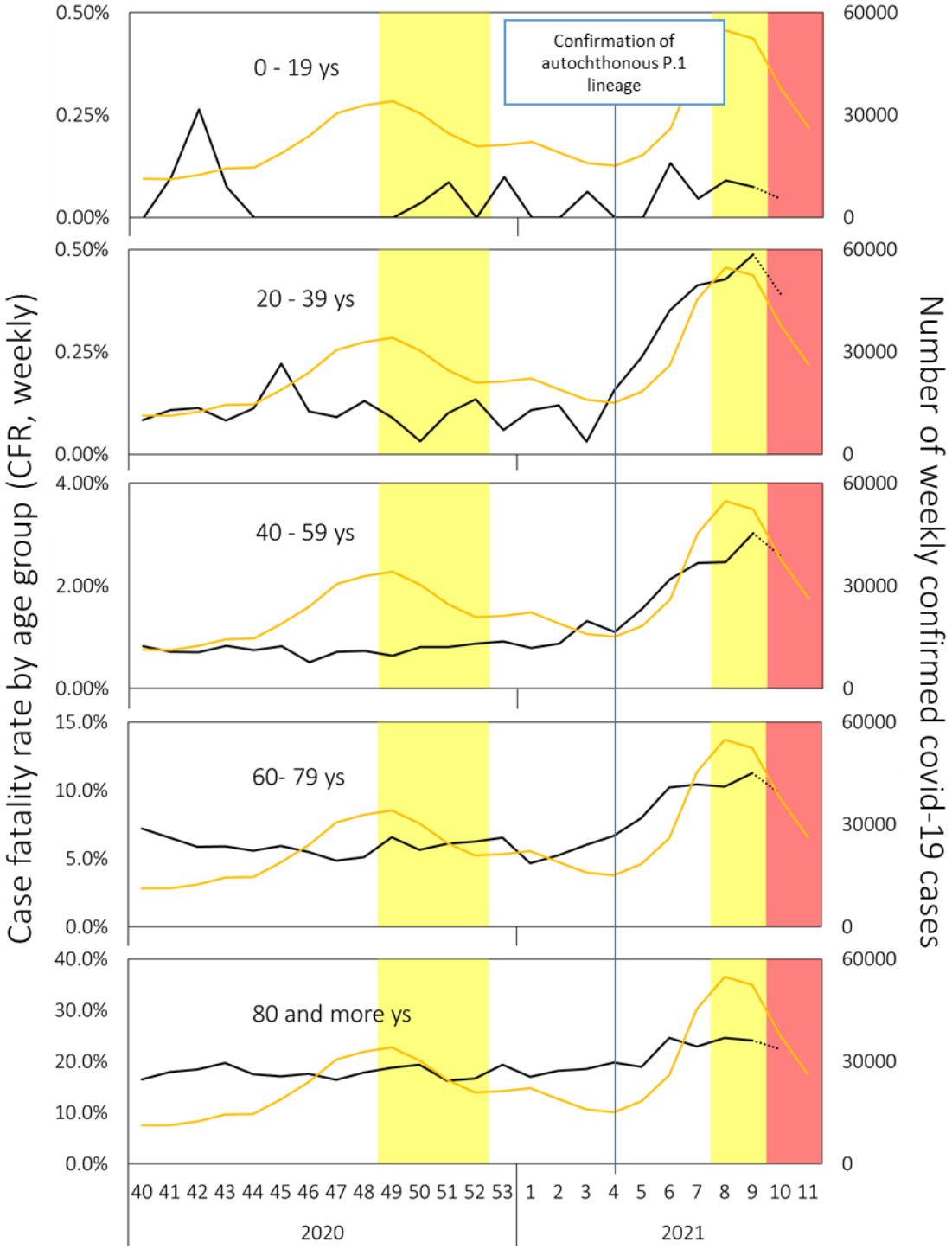

Figure 3: Black line: case fatality rate (CFR, %) of covid-19 confirmed cases according epidemiologic week of symptom onset in Rio Grande do Sul (Brazil) by age group(scale on the left). Orange line: number of weekly confirmed covid-19 cases (scale on the rigth). The yellow area corresponds to the period in which the ICUs were more than 80% full and less than 100% of the capacity, the red area corresponds to the period in which the ICUs were more than 100% of the capacity. Epidemiological week 10 is dotted because the data are not yet definitive.

Supplement:

Confirmed case of COVID-19 by laboratory criteria:
- Detectable result for SARS-CoV-2 performed by the RT-PCR method, which detects in a sample of secretions from the airways (nose and throat) the SARS-CoV-2 virus, which causes COVID-19.

- Reagent result in an immunochromatographic or immunofluorescence antigen test that detects the SARS-CoV-2 virus.

- Reagent result in serological tests (rapid antibody tests, electrochemiluminescence, immunoenzymatic assay, among others), which identify antibodies produced in response to SARS-CoV-2 infection.

Confirmed case of COVID-19 by clinical-epidemiological criteria:
Case of SG or SRAG, without laboratory confirmation, with a history of close or home contact, in the 14 days prior to the appearance of signs and symptoms, with case confirmed laboratory for COVID-19.

Confirmed case of COVID-19 by clinical-image criteria:
Case of SG or SARS or death due to SARS that could not be confirmed by laboratory criteria and that presents tomographic changes indicative of SARS-CoV-2 infection.

Confirmed case of COVID-19 by clinical criteria:
Case of SG or SRAG associated with anosmia (olfactory dysfunction) or ageusia (gustatory dysfunction) without any previous cause and which could not be closed due to another confirmation criterion.

Pre-existing conditions considered at risk

Obesity;
Myocardiopathies of different etiologies (heart failure, ischemic cardiomyopathy, etc.);
Arterial hypertension;
Cerebrovascular disease;
Severe or decompensated lung diseases (moderate / severe asthma, COPD);
Immunodepression and immunosuppression;
Chronic kidney disease in advanced stage (grades 3, 4 and 5);
Diabetes mellitus, according to clinical judgment;
Chromosomal diseases with a weakened immune status;
Malignant neoplasm (except non-melanotic skin cancer);
Hepatical cirrhosis;
Some hematological diseases (including sickle cell anemia and thalassemia);
Pregnancy

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses			Page 3
Methods					
Study Design	4	Present key elements of study design early in the paper			Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Page 3
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 3

Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			Page 3
Bias	9	Describe any efforts to address potential sources of bias			
Study size	10	Explain how the study size was arrived at			Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Page 3
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Page 4
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Page 4
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 4
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest			Table 1

		(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			Table 1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Page 5 and Table 2
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives			
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Page 7
Generalisability	21	Discuss the generalisability (external validity) of the study results			Page 7
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Page 2
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Yes