

Male sex rather than socioeconomic vulnerability as a determinant for COVID-19 death in Sao Paulo: A population-based study

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Abstract

Objectives: To determine the role of the male sex as a risk factor for coronavirus disease deaths in Sao Paulo and to what extent socioeconomic vulnerability and individual health issues can interfere in such risk.

Methods: The primary cause of death, age, sex, comorbidities, and code of the Human Development Units of the residence of 37,583 individuals in Sao Paulo, Brazil, were obtained from the records on confirmed coronavirus disease resident hospitalizations of the city of Sao Paulo from the National Influenza Surveillance Information System. A social vulnerability index was assigned to each Human Development Unit. Using “death” as the outcome variable and sex, admission to the intensive care unit, obesity, renal and heart diseases, diabetes, and social vulnerability as confounders, the odds of death for males and females were compared via logistic regression.

Results: The odds of death for males were 1.242 (confidence interval 95% = 1.237, 1.247) times the corresponding odds for females with the same values for all confounders. We estimated the odds of death for patients living in regions with high social vulnerability as 2.243 (CI 95% = 2.151, 2.339) times the corresponding odds of patients living in regions with very low social vulnerability with the same values of the remaining variables.

Conclusion: The male:female death ratio by severe acute respiratory syndrome coronavirus 2 infection in Sao Paulo cannot be attributed only to comorbidities or social vulnerabilities. Our results suggest that the male sex is an independent biological risk factor for coronavirus disease death. Besides sex-specific factors, further research should focus on crucial biological factors in male sex coronavirus disease mortality.

Keywords

severe acute respiratory syndrome coronavirus 2, coronavirus disease, mortality, men’s health, male sex

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Introduction

More than 2 years after the World Health Organization (WHO) declared the new coronavirus disease (COVID-19) a pandemic, one of the most intriguing unsolved questions is the higher disease burden for males, including hospitalization in intensive care units (ICUs) and death, by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^{1,2}

There are several hypotheses to explain this finding.³ Recently, a study containing data on common metabolic disorders, hospitalizations, and disease prevalence by age, sex, and ethnicity reported that worse COVID-19 outcomes are associated with four underlying medical conditions: obesity,

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diabetes, hypertension, and heart failure.⁴ At a first glance, such outcomes might look like those from other acute infections or chronic health conditions, where male-sex issues represent trigger-points for poor prognosis. Historically men take less care of their own health than women, particularly in countries with high socioeconomic inequalities, where the workload and socio-cultural values impact men's self-care awareness.⁵

COVID-19 sex-disaggregated data are available for more than 3.2 million of a total of 4.5 million deaths up to 24 August 2021, in a universe of 134 million reported cases in 192 countries. Interestingly, based on an unadjusted-for-potential-confounders model,⁶ the male-to-female mean death odds ratio was estimated as 1.7, reaching as high as 3.5 in some countries, regardless of age and infection rates.⁷

Similarly, in another recent meta-analysis addressing global data, the relative risk of fatal outcomes for men relative to women was estimated as 1.63.⁸ It is possible that habits, lifestyles, socioeconomic and cultural backgrounds, and access to healthcare facilities play a role in the higher male COVID-19 fragility, but it is most likely that intrinsic sex-related pathophysiological factors are the causative agents.

The highly populous, extensive, and socially unequal city of Sao Paulo is an ideal environment for this study. Sao Paulo is the primary city of the fourth largest metropolitan area on Earth,⁹ with a population of more than 12 million inhabitants.¹⁰ The city has an expressive absolute COVID-19 death toll, with more than 939,738 confirmed cases and 37,044 confirmed deaths,¹¹ remarkably similar to other global pandemic epicenters, for example, New York city, with its 843,623 confirmed cases and 28,635 confirmed deaths.¹²

Socioeconomic status (SES) is a significant risk factor for dying from COVID-19.¹³ When an external stress on human health occurs (such as a disaster or disease outbreak), social groups are unequally exposed, as has been observed during the COVID-19 pandemic.¹⁴ As an imported disease, the virus first infected people who have traveled abroad and their contacts. In 2 weeks after the first infection, the risk of dying shifted from the highest to the lowest socioeconomic group. People working in essential services or informal work were more exposed. The informal market, which is composed by less educated people, reached 49.7% of the occupied population in 2019. Men were probably more exposed than women in the lower socioeconomic segments, but not in the highest stratum. Thus, it is important to control for SES when studying deaths from COVID-19. Sao Paulo city encompasses all ranges of social vulnerability, and a multicultural and multi-ethnic population representing worldwide inequalities and serving as a reliable model for data gathering. The municipality and State Governments of Sao Paulo have strict and up-to-date computational resources, interconnected with all public and private healthcare institutions, providing real-time data based on daily uploads enabling the generation of a COVID-19 spatiotemporal epidemiological map. This population-based study intends to determine the role of the male

sex as a risk factor for COVID-19 deaths in Sao Paulo, and to what extent socioeconomic vulnerability and individual health issues can interfere with such a risk.

Methods

Study area and data acquisition

Sao Paulo notified the first occurrence of COVID-19 in the country and has had the most important cluster of the disease in Brazil.¹⁵ The Brazilian Amazon region was also important in COVID-19 epidemiology, gaining international relevance due to the high fatality numbers, particularly after the rapid spread of a new SARS-CoV-2 variant of concern (VOC), named P.1. This SARS-CoV-2 VOC was first detected in late November 2020 and carries a unique constellation of mutations confirmed by genomic analysis.¹⁶ The study period chosen, therefore, purposefully included deaths occurred before the P.1 variant emergence.¹⁶

This is an observational, retrospective cross-sectional population-based study. We evaluated secondary data of confirmed deaths from COVID-19 (code B34.2—coronavirus infection disease, according to the International Classification of Diseases Tenth Revision (ICD-10)) among residents of Sao Paulo. The criteria for confirming the cases were clinical, clinical-imaging, clinical-epidemiological, and laboratory. Hospitalization data of confirmed COVID-19 residents were obtained from the National Influenza Surveillance Information System (SIVEP-Gripe) upon a formal request to the Sao Paulo Electronic Information System (e-SIC database, protocol 50161). Data comprised all hospitalizations considering the symptom onset period from 25 February to 21 August 2020. As we had access only to anonymous secondary data with no complete addresses, it was unnecessary to submit this study to the Ethics Committee on Research with Human Beings (as per Resolution No. 510/2016 of the National Health Council) for prior approval.¹³

As data on the individual's SES were commonly absent or defectively filled, we adopted an alternative approach, using residential socioeconomic data. We used the Human Development Units (HDUs) as delineated in the Brazilian Atlas of Human Development as spatial units.¹⁷ The CEInfo technical team geocoded the patients' addresses using its databases and the Google Maps application programming interface (API) geocoding script. Then, the geocoded data were assigned to the 1454 existing HDUs in Sao Paulo, for which demographic and socioeconomic data are consistently and reliably available. To infer the hospitalized person's socioeconomic condition, we used the social vulnerability index (SVI),¹⁷ assigned to each HDU. The SVI is the arithmetic mean of the following dimension indices: urban infrastructure, human capital, income, and labor, summarizing the most important and relevant aspects of the socioeconomic context. Thus, the database included the primary cause of death, age, sex, date of death, the presence of underlying medical conditions, comorbidities, and the

HDU of the patient's residence. The SIVEP-Gripe system has been gradually adapted to collect specific information for the pandemic emergency. Several fields were added to allow recording of auto-reported comorbidities (the condition of having another disease when the person acquired COVID-19).

Statistical analyses

The data set contained 43,214 records, out of which 37,583 had information regarding recovery or death related to COVID-19. We selected the following variables for analysis: age (years), sex (male or female), ICU admission (yes or no), obesity (yes or no), renal disease (yes or no), heart disease (yes or no), diabetes (yes or no), admission period (week since first detected case, classified according to quartiles (11 or less, 12–21, 22–26, 27 or more)) and social vulnerability, classified according to the SVI as follows (very low ($SVI < 0.200$), low ($0.200 \leq SVI < 0.300$), medium ($0.300 \leq SVI < 0.400$), high ($0.400 \leq SVI < 0.500$), very high (≥ 0.500)).¹⁸

Summary statistics were computed for the selected variables. Using COVID-19-related death as the outcome and sex as the target risk factor, the odds ratio of COVID-19-related deaths for males and females was evaluated via logistic regression models having admission to the ICU, obesity, renal disease, heart disease, diabetes, and social vulnerability as confounders. Although there is missing data on confounding variables (comorbidities) because this field was not mandatory, filling was random. There was no missing data for sex and outcome (recovery or death). Thus, this analysis is considered unbiased because missingness in any variable in the model is not related to the outcome.¹⁹ In addition, to account for a possible bias associated with missing data, we computed the corresponding male-to-female proportions for each variable. To evaluate the stability of the coefficient related to the target risk factor (sex), we compared the full model with different models, starting with a crude model containing sex as the single predictor and sequentially adding the remaining predictors. A sensitivity analysis involving the comparison of the adopted model with a model including the interaction between sex and vulnerability was done. For these analyses, we used the R statistical software.

Ethics statement

Since we had access only to anonymous secondary registers with no detailed addresses, it was unnecessary to submit this study to the Ethics Committee on Research with Human Beings (as per Resolution No. 510/2016 of the National Health Council, Brazil) for prior approval.²⁰

Results

Figure 1 shows a flowchart illustrating the registered hospitalizations, exclusion criteria, and respective number of

deaths and recoveries used for analysis. The sex-disaggregated, clinical, and demographic population characteristics are displayed in Table 1. The maximum difference between the proportions of missing values for males and females was 4.1% (56.0% for males and 51.9% for females). Coefficients, sample sizes, Akaike information criterion (AIC), and the estimated male:female COVID-19-related death odds ratios for fitted logistic regression models are displayed in Table 2. The male:female COVID-19 death ratios across the city are depicted in Figure 2.

The model adopted (Model 9) was compared to a model with additional sex multiplied by social vulnerability interaction to evaluate whether the sex odds ratio would change with social vulnerability. A likelihood ratio test did not support such interaction ($P=0.778$). Therefore, we conclude that the sex odds ratio is constant across the different categories of social vulnerability. The results suggested that the odds ratio of COVID-19-related death for males is 1.242 (confidence interval (CI) 95%=1.237, 1.247) times the corresponding odds ratio for females with the same conditions for the confounders, namely: age, admission to ICU, obesity, renal diseases, heart disease, diabetes, admission period, and social vulnerability.

Although social vulnerability did not significantly change the COVID-19-related death odds ratio, a byproduct of the analysis indicated that the odds ratio of death for patients living in regions with low social vulnerability is 1.769 (CI 95%=1.755, 1.784) times the corresponding odds ratio of patients with the same levels of the remaining confounders living in regions with very low social vulnerability. Second, the odds ratio of death for patients living in regions with medium social vulnerability is 2.020 (CI 95%=2.005, 2.035) times the corresponding odds ratio of patients with the same levels of the remaining confounders living in regions with very low social vulnerability. Finally, the odds of death for patients living in regions with high social vulnerability is 2.243 (CI 95%=2.151, 2.339) times the corresponding odds ratio of patients with the same levels of the remaining confounders living in regions with very low social vulnerability.

Discussion

This research highlights that the male:female death ratio by SARS-CoV-2 infection in Sao Paulo cannot be attributed only to comorbidities or social vulnerabilities. Our results suggest that the male sex is an independent biological risk factor for COVID-19 death. We explored sex-disaggregated data and coefficients in logistic regression models for death by sex by sequentially adding confounders, such as age, underlying medical conditions, the period of infection in the pandemic timeline, and a social vulnerability index. The fact that males die more than females from COVID-19 deserves further attention.

Since the first episode of the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East

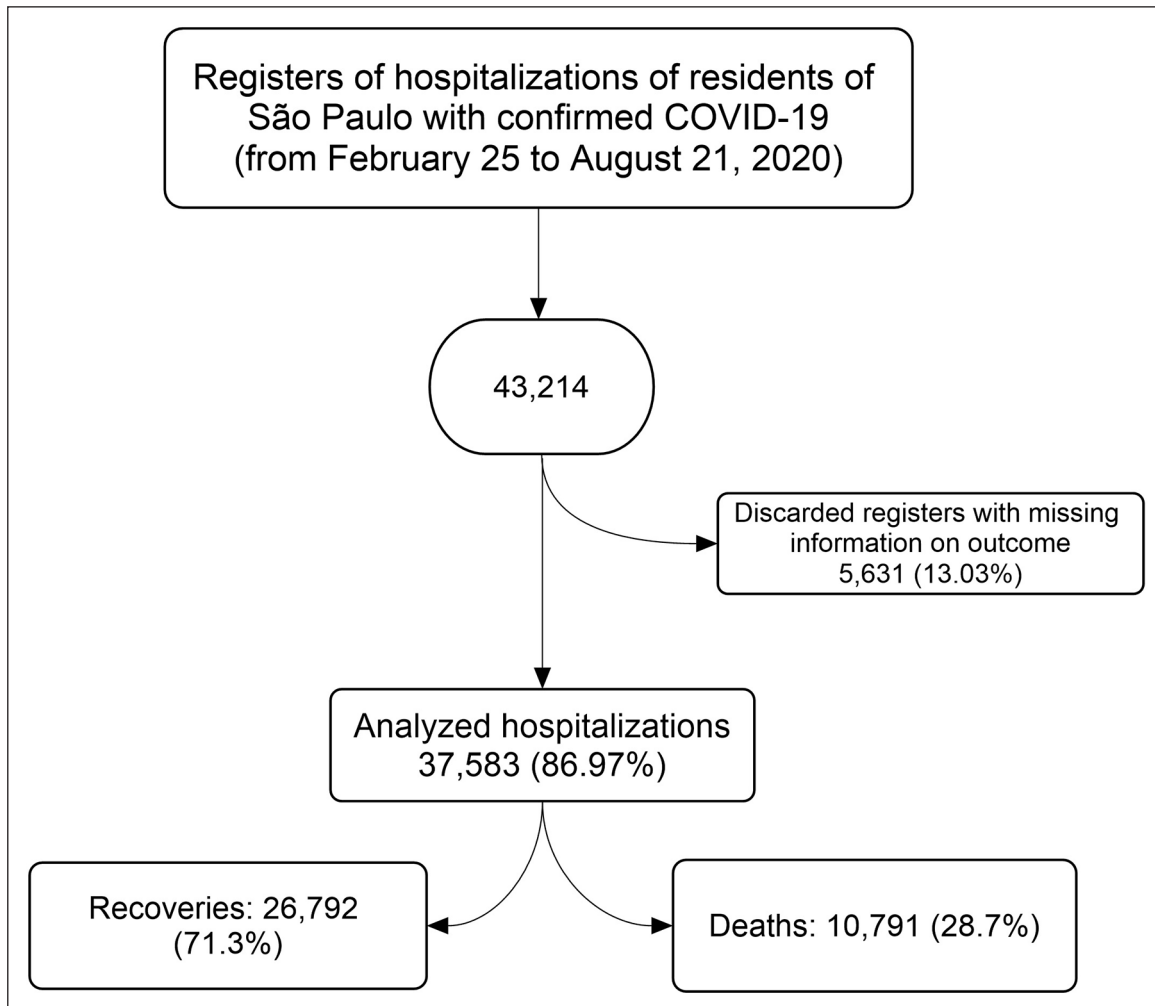


Figure 1. Registers of hospitalizations, residents, City of São Paulo, Brazil; data source: Epidemiology and Information Coordination Center (CEInfo), São Paulo Health Secretariat (SMS-SP). State of São Paulo Electronic Information System (e-SIC database, protocol 50161).

respiratory syndrome coronavirus (MERS-CoV), men were more likely to experience worse outcomes.²¹ Intriguingly, the male:female mortality ratio is quite ubiquitous. Notably, we are still far from understanding the multiplicity of factors related to the staggeringly higher fatalities in males. According to Global Health 5050 data, the ratio of male:female COVID-19 confirmed cases and deaths is higher than one in 99 out of 106 countries that report sex-disaggregated data, except for India, Australia, Finland, Vietnam, Iraq, Uganda, and Yemen.⁷

The lower male:female ratios found in a few countries has been surprising in the global data context. Possible explanations might include demographic factors, data quality, or women's baseline health profile, suggesting different exposure profiles to SARS-CoV-2.²² In many countries, sex impacts access to economic resources and sex inequality may be a barrier to access healthcare.²³ Also, acute malnourishment among women and children in countries after prolonged conflict periods may pose a severe burden.²⁴ Furthermore, the variable access to SARS-CoV-2 infection diagnostics by population subgroups, and the fact that only

hospitals report fatalities in some regions, are likely to result in sex biases in the COVID-19 death toll.²⁴

Several hypotheses try to explore why males are prone to worse outcomes after SARS-CoV-2 infection. In a recent systematic review of 47 studies reporting over 21,000 deaths in China, male unadjusted mortality rates were higher than those of females. The proportion of females presenting severe disease and admitted to ICUs was also lower than that of men. However, adjusted analyses were not conclusive due to data paucity.²⁵ In another recent systematic review and meta-analysis to assess sex differences in the prevalence of COVID-19 confirmed cases, using a total of 57 studies with over 221,000 participants, the pooled prevalence of COVID-19 among males and females was reported as 55.00% (CI 95%=51.43, 56.58) and 45.00%, respectively, indicating higher prevalence among males. The authors proposed that the likely cause of sex disparity may be related to behavioral and societal factors. Supposedly, male sex individuals have more risk factors for exposure to SARS-CoV-2 and development of severe disease, like

Table 1. Baseline sex-disaggregated, clinical and demographic population features —March to August 2020, Sao Paulo, Brazil.

	Male	Female
N	20,570	16,832
Age		
Mean (S.D.)—years	58.00 (\pm 17.00)	60.00 (\pm 19.00)
Deaths—n (%)		
COVID-19	6133 (29.90%)	4658 (27.70%)
Other causes	7 (<0.01%)	2 (<0.01%)
Social vulnerability index (SVI)—n (%)		
Very low	4843 (23.34%)	3834 (22.78%)
Low	6200 (29.88%)	4969 (29.52%)
Medium	8806 (42.43%)	7249 (43.07%)
High	470 (2.26%)	442 (2.63%)
Missing values	434 (2.09%)	336 (2.00%)
Admission period—n (%)		
1	7 (0.03%)	6 (0.04%)
2	10,849 (52.28%)	8394 (49.88%)
3	5232 (25.21%)	4464 (26.52%)
4	4665 (22.48%)	3966 (23.57%)
Missing values	0 (0.00%)	0 (0.00%)
Intensive care unit—n (%)		
Yes	7386 (35.59%)	5269 (31.31%)
No	11,733 (56.54%)	10,173 (60.45%)
Missing values	1634 (7.87%)	1388 (8.23%)
Obesity—n (%)		
Yes	1161 (5.59%)	1080 (6.42%)
No	5618 (27.07%)	4817 (28.62%)
Missing values	13,974 (67.33%)	10,933 (64.96%)
Renal disease—n (%)		
Yes	1092 (5.26%)	693 (4.12%)
No	5869 (28.28%)	5226 (31.05%)
Missing values	13,792 (66.46%)	10,911 (64.83%)
Heart disease—n (%)		
Yes	7776 (37.46%)	6913 (41.08%)
No	2717 (13.09%)	2376 (14.12%)
Missing values	10,260 (49.44%)	7541 (44.81%)
Diabetes mellitus—n (%)		
Yes	5306 (25.57%)	4679 (27.80%)
No	3834 (18.47%)	3415 (20.29%)
Missing values	11,613 (55.96%)	8736 (51.91%)

SD: standard deviation; COVID-19: coronavirus disease.

smoking, alcohol consumption, exposure during burials, work in primary sectors with increased occupational hazards that demand physical activity outside their homes, and a greater degree of interaction, among others.²⁶ In another study, men's low hygienic habits, low hand-washing, absence from home, and sitting closer to other people removing their masks to drink and smoke are arguments for an increased level of exposure, increased risk of infection, and disease severity.²⁷ The literature is prolific in advocating that comorbidities, such as cardiovascular disease, hypertension, obesity, diabetes, metabolic syndrome, stress, and anxiety, with less attention both by the healthcare system and the individuals themselves, are determinant factors to explain

increased male vulnerability to viruses.²² In a study in New York City, men were associated with higher hospitalization than women. They were considerably more likely to present comorbidities than people not admitted to the hospital and to have cardiovascular disease, diabetes, and chronic kidney disease. In an uncontrolled multivariate analysis, factors most strongly associated with hospital admissions were male sex, age of 65 years or older, heart failure, chronic kidney disease, increased body mass index, and hypertension.¹ These behavioral determinants for men's lower overall general health status tend to underscore potentially biologically intrinsic sex-driven mechanisms underlying males' poor outcomes way beyond socio-behavioral-chronic issues.

Table 2. Logistic regression models' coefficients for deaths by sex with sequentially added variables (age, underlying medical conditions, epidemiological periods, and social vulnerability indexes).

	1	2	3	4	5	6	7	8	9
Sex	0.092	0.301	0.210	0.210	0.192	0.200	0.201	0.194	0.217
Age		0.056	0.057	0.049	0.048	0.048	0.048	0.049	0.054
ICU			1.621	1.501	1.479	1.480	1.474	1.496	1.530
Obesity				0.218	0.319	0.324	0.320	0.344	0.383
Renal disease					0.768	0.773	0.778	0.779	0.783
Heart disease						-0.025*	-0.031*	-0.022*	-0.035*
Diabetes mellitus							0.140	0.135	0.103
EP 2								-2.227	-2.502
EP 3								-2.540	-2.812
EP 4								-2.935	-3.204
Low SVI									0.571
Medium SVI									0.703
High SVI									0.808
N	37,583	37,555	35,534	12,239	11,203	11,166	11,122	11,122	10,896
AIC	450.54	390.06	323.72	135.00	123.16	122.76	122.29	120.74	116.98
(M:F) OR	1.096	1.351	1.234	1.233	1.212	1.221	1.223	1.214	1.242

ICU: Intensive care unit; EP: epidemiological period; SVI: social vulnerability index; n: sample size; AIC: Akaike information criterion; (M:F) OR: estimated male/female odds ratio; *= $p > 0.05$.

A non-randomized control trial in Rio de Janeiro, Brazil, that assessed whether socioeconomic status determines the risk of death by SARS-CoV-2 infection suggests that male sex is an independent influencer of disease severity and an independent risk factor for death. Concomitantly, people with less formal education and non-white ethnicity present a higher mortality risk.²⁸ Unfortunately, the reader might interpret that being a male or belonging to a lower socioeconomic stratum explains the male bias; this interpretation might guide policymakers to ineffective public policies.²⁸ Furthermore, Bermudi et al.¹³ in an ecological study in Sao Paulo reported that higher mortality in males increases with aging.

Similarly, Ribeiro et al.²⁹ demonstrated an 84% increased COVID-19 mortality risk in men relatively to women in Sao Paulo, a result higher than the one we obtained via logistic regression models. The difference between these two results might reflect the number of control variables used in each model. In ours, we progressively added seven control variables, including the five most relevant underlying medical conditions for COVID-19, the pandemic epidemiologic period, and a social vulnerability index, suggesting a more robust conclusion. Moreover, this difference can also be explained by the fact that Ribeiro et al. used data of both confirmed COVID-19 (ICD10 code B34.2) and suspected cases (ICD10 code U04.9).

Although men living in high social vulnerability areas presented an elevated odds ratio of death compared to those living in lower socioeconomic vulnerability areas, data from our regression model revealed that the male:female ratio remained unchanged. This finding is significant in strengthening disease-risk governance to manage with

more precisely disregarded issues that could help mitigate future outbreaks and guide public health strategies, including prioritizing more sensitive male-sex risk subgroups with higher social vulnerability indexes.

Several biological mechanisms were hypothesized to justify male vulnerability to SARS-CoV-2 infection. It is unclear if males are more likely to get infected and develop severe disease, whereas females may have intrinsic protection against SARS-CoV-2. Men enduring infectious sepsis have a 70% higher mortality than women,³⁰ and studies on other coronavirus-related diseases, such as SARS and MERS, reveal similar findings.³¹ SARS-CoV-2 human cell invasion involves the role of two co-receptors, the angiotensin-converting enzyme 2 (ACE2) and the transmembrane serine protease 2 (TMPRSS2).³² The difference in ACE2 and TMPRSS2 genetic expressions in immunologic responses and their endocrine regulation probably exert essential roles in specific male responses to SARS-CoV-2 infection.^{33,34} Therefore, further studies are needed to elucidate which biological mechanisms explain the worse COVID-19 outcomes in the male sex.

This study presents a potential bias for residual or unmeasured confounding factors, and also possible biases associated with missing data, for example, imputation or some bias analysis. Entirely at random missing data were addressed by "listwise deletion." Since we used all the data that are available (the entire hospitalized population), there would be no need to estimate the effect since the power is 100% because any effect will be detected. Furthermore, if the study measures the entire population, there is no danger of the sample being a poor estimate of the population.³⁵ Nonetheless, our final sample was significant enough to minimize the probability of generating false null results.

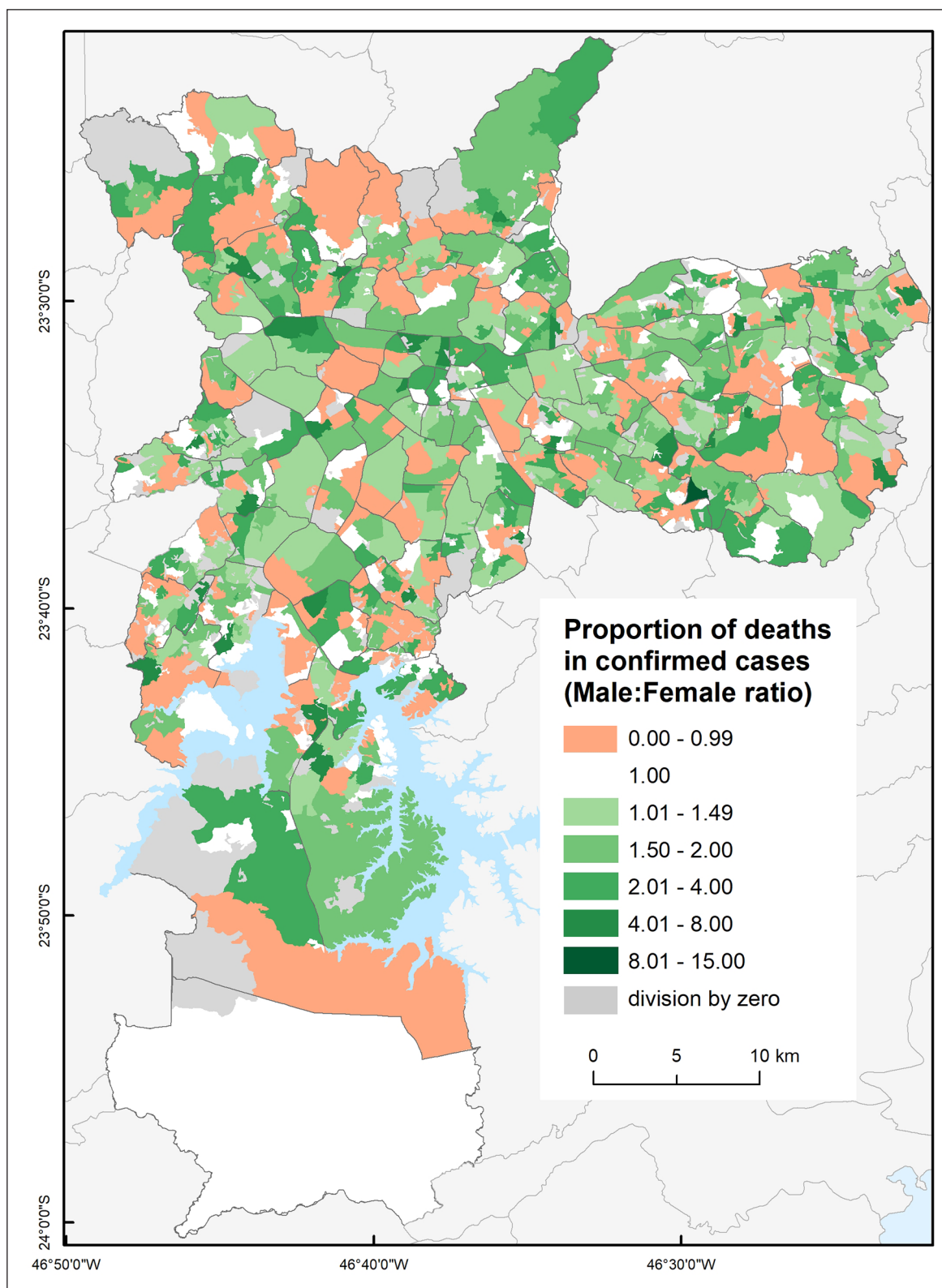


Figure 2. Male: female ratio of deaths of reported COVID-19 cases, City of São Paulo, Brazil, by Human Development Unit; data source: Mortality Information Improvement Program (PRO-AIM), Epidemiology and Information Coordination Center (CEInfo), São Paulo Health Secretariat (SMS-SP). Data obtained through a formal request to the São Paulo Electronic Information System (e-SIC database, protocol 50161).

Although relevant as potential confounder in the observed association between sex and COVID-19 deaths, ethnicity was not considered in our analyses because the ignored or missing values in this database field corresponded to 12,969 patients (about 35% of hospitalizations).

Conclusion

In this study, we observed a higher male:female COVID-19-related death odds ratio in Sao Paulo, Brazil, and hypothesized that these findings could not be exclusively attributable to socioeconomic, behavioral, and cultural status, nor underlying comorbidities and social vulnerability status. We demonstrate that the most critical determinants of severe outcome and death by COVID-19, such as comorbidities, incidence during different periods of the pandemic, and socioeconomic vulnerability indexes cannot explain excess male deaths. Therefore, biological factors seem crucial to explain our findings of increased male frailty to COVID-19 in Sao Paulo and should promote future research to prove this hypothesis, generalize it worldwide, and guide public policies toward male sex vulnerability.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval

Ethical approval was not sought for the present study because, as we had access only to anonymous secondary registers with no point addresses, it was unnecessary to submit the study to the Ethics Committee on Research with Human Beings (as per Resolution No. 510/2016 of the National Health Council).

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Informed consent

Informed consent did not apply due to the nature of the study: only secondary data were obtained from an Electronic Information System.

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