Examining socio-economic factors to understand the hospital case fatality rates of COVID-19 in the city of São Paulo, Brazil

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Background: Understanding differences in hospital case fatality rates (HCFRs) of coronavirus disease 2019 (COVID-19) may help evaluate its severity and the capacity of the healthcare system to reduce mortality.

Methods: We examined the variability in HCFRs of COVID-19 in relation to spatial inequalities in socio-economic factors, hospital health sector and patient medical condition across the city of São Paulo, Brazil. We obtained the standardized hospital case fatality ratio adjusted indirectly by age and sex, which is the ratio between the HCFR of a specific spatial unit and the HCFR for the entire study area. We modelled it using a generalized linear mixed model with spatial random effects in a Bayesian context.

Results: We found that HCFRs were higher for men and for individuals ≥60 y of age. Our models identified per capita income as a significant factor that is negatively associated with the HCFRs of COVID-19, even after adjusting for age, sex and presence of risk factors.

Conclusions: Spatial analyses of the implementation of these methods and of disparities in COVID-19 outcomes may help in the development of policies for at-risk populations in geographically defined areas.

Keywords: Bayesian spatial analysis, comorbidities, coronavirus, modelling

Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on 11 March 2020. Since then, several vaccines have been developed and authorized for use by the WHO and countries are in various stages of developing national immunization plans. However, these plans will follow different implementation processes and some countries will take longer to reach their immunization goals. Furthermore, once these goals are achieved, it will take time to determine the levels of protection actually afforded by the vaccine under real-life conditions. Therefore, rather than relying completely on vaccines, risk factors related to the lethality of COVID-19 need to be identified and mitigated. In countries such as Brazil, which has only performed testing at a rate of 11.3 per 100 000 inhabitants, the overall case fatality rate (CFR) is overestimated because tests end up being done only for more severe cases of the disease. Although it is impossible to know the real impact of COVID-19 fatalities in Brazil, estimating fatality rates based on confirmed hospital cases allows for the identification of specific at-risk populations. In particular, differences in hospital case fatality rates (HCFRs) may help evaluate both differences in the severity of the disease across the board and also the capacity of the healthcare system to reduce COVID-19 mortality. Unlike morbidity, which depends on the virus’ contagiousness, CFRs are dependent on the virulence of the virus. Viral load, biological risk, population vulnerability (e.g. age structure, prevalence of comorbidities), health system efficiency, healthcare accessibility and disease detection capacity are the most important factors associated with disease lethality. Thus the present study aimed to assess the association of socio-economic factors, hospital health sector and patient...
medical condition with the spatial variability of COVID-19 HCFRs in the city of São Paulo (SP), Brazil.

**Methods**

**Study area and data acquisition**

This ecological study was based on confirmed COVID-19 hospitalizations, independent of outcome, occurring in SP hospitals from 27 February to 19 November 2020. The study population was restricted to hospitalized SP residents registered in the National Influenza Surveillance Information System (Sivep-Gripe; extraction date 24 Nov 2020).

We used spatial analysis methods to compare HCFRs in sociodemographically distinct regions of SP. The CEInfo, a division of SP’s Health Secretariat, geocoded the residential addresses of COVID-19 patients, assigned them to a Human Development Unit (HDU) and created an anonymized database. This database was provided by formal request to the São Paulo Electronic Information System (e-SIC, protocol 53197). As the database was limited to secondary, anonymized data aggregated by HDUs, study approval was not required from the Ethics Committee on Research with Human Beings in accordance with Resolution No. 510/2016 of the National Health Council.5

SP is the capital of the Brazilian state of São Paulo and is the primary city in the largest metropolitan area of the southern hemisphere. We used HDUs, as delineated in the Brazilian Atlas of Human Development,7 as the geographic unit of aggregation. HDUs are homogeneous socio-economic areas based on information garnered from the 2010 Brazilian Demographic Census.8 Inside its urban area, SP contains 1594 HDUs. In relation to per capita income, we converted the values from Brazilian reals (BRL) to UK pounds (GBP; conversion rate 1 GBP=2.74 BRL). We used the values in effect in 2010.9 Patient demographic and medical information was obtained from the Sivep-Gripe database. Only records with information on patient age, sex, HDU, date of hospitalization and outcome date were included in the analysis. We calculated the observed sex- and age-specific HCFRs for each HDU, using direct age and sex standardization. We also obtained the expected deaths for each HDU, which were derived through indirect age and sex standardization.10 The expected values were used as offsets in our geospatial models, allowing us to interpret our results as relative risks (RRs) and to obtain the adjusted standardized hospital case fatality ratios (SHCFRs) for each HDU. These values are strictly related to the HCFRs and represent, for a specific HDU, the ratio between the HCFR of the spatial unit and the HCFR for the entire study area, considering the age and sex distribution of those hospitalized with COVID-19 and those who died.

**Data analysis and modelling**

The observed and expected COVID-19 deaths were linked to HDU shapefiles using the HDU codes. We modelled the number of COVID-19 deaths using a Poisson probability distribution and latent Gaussian models.11 We used the Besag–York–Mollie (BYM) model12 with the parametrization proposed by Riebler et al.13 It has two components: the first is composed by a structured spatial random effect with a conditional autoregressive (CAR) structure that considers the neighbourhood relationship among the spatial units (i.e. HDUs). We used a Queen contiguity weight matrix to represent the HDU neighbourhood relationship, which is one of the geometric matrices whose scheme is spatially contiguous neighbours defined as two polygons that share a common boundary or vertex.14 The second component of the BYM model is an unstructured random effect independent and identically distributed that models the uncorrelated noise.12 We ran the models in a Bayesian hierarchical context with integrated nested Laplace approximations (INLAs).15,16 We first ran a model only with the intercept and the structured and unstructured spatial random effects to be used as a basis for comparison for the other models we ran.

We identified HDU-specific socio-economic variables from the Atlas of Human Development database, limiting the selection to those that were not constructs of original fields (see Supplementary Material 1). We used the Cleveland plot to identify outliers17 and transformed covariates with them using a square root or logarithm. Covariates were standardized to a mean of 0 and a standard deviation (SD) of 1. Then we used a principal component analysis to identify a smaller group to test in the models. For each principal component with an eigenvalue > 1, we selected the four covariates with the highest loading and ran models with intercept, structured and unstructured spatial random effects and each one of these four covariates against the observed COVID-19 deaths. We retained, for each one of the considered principal components, the covariate with the lowest deviance information criterion (DIC) in the modelling. In addition to the HDU-level socio-economic fields, using the Sivep-Gripe database, we used an individual-level variable for private health insurance and an aggregate indicator for the percentage of patients with one or more of the medical risk factors (‘yes’ represented at least one risk factor and ‘no’ represented no risk factor). Risk factors considered were at least one comorbidity/condition listed in the Sivep-Gripe database: postpartum, chronic cardiovascular disease, chronic haematological disease, Down syndrome, chronic liver disease, asthma, diabetes mellitus, chronic neurological disease, other chronic pneumopathology, immunodeficiency or immunodepression, chronic kidney disease and obesity. Once we had the set of covariates to run our final model, we did an exploratory analysis to identify and avoid collinearity.

Once we defined the covariates that would be in our final model, we ran it also considering the intercept and the spatial random effects. We obtained the predicted SHCFRs for each one of the HDUs and presented them as a map. We obtained the respective RRs and their 95% confidence intervals (CIs) for the considered covariates. We evaluated the behaviour of the standardized residuals of our final model against the fitted values, then mapped and tested them to spatial autocorrelation using Global Moran I. We also investigated the role of the covariates in explaining the spatial autocorrelation of COVID-19 deaths. To do this, we first obtained the posterior mean of the spatial random effects, which were exponentiated and presented as RRs for the model without covariates (our first model). In the sequence, we obtained the spatial random effects for the model with the socio-economic covariates and, finally, the spatial random effects for our final model. Since we had these values for each HDU, we presented them as maps. We considered non-informative priors for the fixed effects and penalized complexity priors for the random
### Table 1. Distribution of HCFRs by age and sex for the city of São Paulo, 27 February–19 November 2020

| Age group (years) | Male          |          | Female |          | Overall |          |
|------------------|---------------|----------|--------|----------|---------|----------|
|                  | Deaths | Hospitalizations | HCFR, % | Deaths | Hospitalizations | HCFR, % | Deaths | Hospitalizations | HCFR, % |
| 0–19             | 16     | 372      | 4.3  | 17      | 381      | 4.5     | 33      | 753      | 4.4    |
| 20–39            | 275    | 3 300    | 8.3  | 162     | 2 792    | 5.8     | 437     | 6 092    | 7.2    |
| 40–59            | 1 368  | 8 924    | 15.3 | 800     | 5 768    | 13.9    | 2 168   | 14 692   | 14.5   |
| ≥60              | 5 205  | 11 745   | 44.3 | 4 316   | 10 866   | 39.7    | 9 521   | 22 611   | 42.1   |
| Total            | 6 864  | 24 341   | 28.2 | 5 295   | 19 807   | 26.7    | 12 159  | 44 148   | 27.5   |

### Table 2. Posterior means of the RRs and 95% CIs for the covariates in the spatial model for death in COVID-19 hospitalized people, municipality of São Paulo, state of São Paulo, Brazil, from 27 February to 19 November 2020

| Covariate                                      | RR   | 95% CI       |
|------------------------------------------------|------|--------------|
| Intercept                                      | 1.03 | 1.01 to 1.05 |
| Per capita income (in log scale)*              | 0.91 | 0.87 to 0.95 |
| Percentage of employed people >18 y of age who work in the formal sector | 1.00 | 0.97 to 1.03 |
| Percentage of children 0–5 y of age who do not attend school | 0.99 | 0.97 to 1.01 |
| Percentage of people living in households with per capita income less than half the minimum wage who commute [or travel] more than 1 h to work | 1.00 | 0.97 to 1.02 |
| Percentage of people hospitalized for COVID-19 in private hospitals | 0.97 | 0.93 to 1.01 |
| Risk factor rate of hospitalized people         | 1.11 | 1.06 to 1.15 |

*The values of per capita income are based on the mean monthly income per capita in 2010 GBP.*

### Results

After excluding records for non-SP residents and hospitals, records for patients with confirmed medical diagnoses other than COVID-19 and 29 records without information for patient age, a total of 44 148 records were available for analysis. For the entire municipality of SP, a total of 12 159 COVID-19 deaths were confirmed, representing an overall HCFR of 27.5%. Men accounted for 55.1% of hospitalizations and 56.4% of deaths and had an HCFR of 28.2% (compared with 26.7% for women). The percentages of hospitalizations and deaths as well as HCFRs increased with age; all values were higher for men except for the youngest age group. Table 1 indicates the variation of HCFRs by age and sex.

From the 1594 HDUs of SP, 140 did not have any reported COVID-19 hospitalizations (Supplementary Material 6). Since we intended to model the COVID-19 deaths among the hospitalized cases using a Poisson probability distribution and to obtain the adjusted SHCFRs, we needed to avoid zeros as expected deaths. We solved this issue by merging these 140 HDUs into adjacent HDUs with which they shared the largest contiguous border, resulting in 1454 HDUs. In the sequence, we calculated the raw SHCFRs and identified two HDUs with outliers, each one with one death and few COVID-19 hospitalized cases. We used the same approach presented above and merged these two HDUs into adjacent ones. We also included the deaths and cases of the previous HDUs into the new ones. After doing these procedures, the number of spatial units was 1452 HDUs.

We found five principal components with eigenvalues >1 and selected five socio-economic covariates, as presented in our Methods section. We joined them with the percentage of people hospitalized for COVID-19 in private hospitals and the risk factors rate of hospitalized people and evaluated the collinearity among them. Two of the socio-economic covariates presented collinearity (Pearson correlation coefficient=0.92): percentage of people ≥18 y of age who have completed elementary school and per capita income. Between them, we chose the last one because it presented the lowest DIC value. This covariate was transformed by applying the logarithm because of the existence of outliers. The set of covariates we included in our final model is presented in Table 2.

Figure 1 shows the spatial distribution of the COVID-19 HCFRs, the predicted SHCFRs, per capita income (monthly average value) and risk factor rate of hospitalized people covariates. Considering the HCFRs (Figure 1A), there was an indication of higher risk in the peripheral regions of the municipality. However, the SHCFRs demonstrated smoother patterns and the higher rates in the peripheral regions were more noticeable (Figure 1B). Figure 1C...
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Figure 1. Study area and (A) COVID-19 HCFR (%), (B) posterior means of the predicted SHCFRs for COVID-19, (C) per capita income (monthly, in GBP) and (D) risk factor rates of hospitalized people. HDUs of the municipality of São Paulo, state of São Paulo, Brazil, from 27 February to 19 November 2020. The boundaries of the administrative district (AD) are also indicated on the maps, as they are widely used by health managers. The values of per capita income are based on the mean monthly income per capita in 2010 GBP.

shows higher income in the central regions, and there is a suggestion of an inverse association with death among the COVID-19 hospitalized people. Analysing Figure 1D, the spatial patterns of the risk factor rates of hospitalized people were similar to those of the fatality rates, suggesting a direct association. Table 2 provides the posterior means of the RRs and the 95% CIs for the considered covariates in the modelling of COVID-19 death, adjusted by the spatial autocorrelation. Two covariates were significantly associated with deaths among COVID-19 hospitalized people in the adjusted model: per capita income (in log scale) had a negative association (RR 0.91 [95% CI 0.87 to 0.95]) and risk factor rate of hospitalized people had a positive association (RR 1.11 [95% CI 1.06 to 1.15]). The increase of 1 SD in each one of these two covariates would result in a decrease of 9% and in an increase of 11% in the risk of death among COVID-19 hospitalized people, respectively.

Figure 2 shows, for the HDUs, the posterior mean of the spatial random effects (exponentiated and presented as RR) for the model without covariates (Figure 2A), the model with socio-economic covariates, including the first four in Table 2 and for the final model, including all covariates of Table 2 (Figure 2C). Comparing these three maps, one can see that the spatial risk in the first model ranged from 0.79 to 1.23 and that the values below the unit were in the centre of the city and those above were in the peripheral areas. After adjustment for the socio-economic covariates, the range of the values of the spatial risk shrank to 0.95–1.06 and became almost the same in the entire city. Thus we can say that the socio-economic covariates explained a great part of the spatial autocorrelation that was present in our response variable.

Finally, we evaluated the residuals of our final model, which we present in Supplementary Material 7. The plot of the standardized
residuals against the fitted values showed that our model was well adjusted, with the residuals randomly dispersed around the zero, constant variance, values concentrated between −2 and 2 and few values >3. The residual map showed that the residuals were randomly distributed in the space, which was confirmed by Global Moran I (equal to 0.008 and not significant).

Discussion

The results of the present study indicated an overall HCFR of 27.5% for the area of the city of São Paulo, similar to results from China for a retrospective cohort of 191 patients at two hospitals. Few studies to date have reported on the main factors associated with fatality rates in hospitalized patients. Regarding age and sex, we found that the fatality rate was higher in men and in those ≥60 y of age, similar to what was found in other studies. In China, across all age groups, the death rate among confirmed cases was approximately 2.8% for women and 4.7% for men. Even in countries such as Spain (49%) and Switzerland (47%), which have reported fewer infections in men than in women, men accounted for 63% and 62% of deaths, respectively (based on statistics from mid-April 2020). It is well known that men and women differ in terms of risk and severity for diseases involving the immune system. Women are disproportionately affected by autoimmune disorders, while men tend to be more susceptible to infectious diseases, both in terms of prevalence and the severity of the disease. The reasons for sex-based differences in COVID-19 are likely multifactorial and include genetics, lifestyle differences, comorbidities and hormones.

Our models found spatial variations in socio-economic factors, especially per capita income, to be associated with variations in COVID-19 HCFRs across the SP municipal area. This suggests that a reduction in socio-economic disadvantage could contribute to a decreased risk of COVID-19-related mortality, which is supported by the shrinking of the spatial random effects after adjustment for socio-economic covariates. Corburn et al. suggested measures to protect dwellers of informal urban housing, homeless people and those living in precarious environments from exposure to COVID-19. Residents of extremely impoverished areas should be prioritized in vaccine distribution policies. A number of studies have offered empirical evidence regarding the association of human health factors, including physical and mental health, with adverse socio-economic factors, such as poverty, unemployment and occupational risks, and have shown these to be associated with negative health outcomes. Socio-economically disadvantaged people are also more likely to have decreased access to healthcare, healthy food or recreational facilities, a lower level of physical activity, higher use of alcohol and/or tobacco and less knowledge of healthy living standards.

One important limitation of our study is that it is based on secondary data from the Sivep-Gripe database. It is a passive surveillance system and is subject to subnotification. Consequently, our study could have some type of information bias, for example, the non-detection of hospitalized COVID-19 cases in parts of the HDUs. Apart from this limitation, we used modelling methods in accordance with the assumptions of regression modelling, enabling us to obtain validity results. The use of latent Gaussian models in a Bayesian approach with the BYM configuration allowed us to show the relationship between COVID-19 deaths and the considered covariates and to depict the role of the socio-economic conditions as an important determinant of the spatial pattern of the occurrence of deaths among hospitalized COVID-19 patients.

Conclusions

The results of the present study indicated that socio-economic conditions could have a significant relationship with HCFRs in large cities such as SP. In particular, our spatial analyses showed that areas of SP with the highest socio-economic levels have the
lowest COVID-19 fatality rates. Enhanced testing, contact tracing, social distancing and self-isolation are particularly needed in vulnerable communities. Spatial analyses of the implementation of these methods and of disparities in COVID-19 outcomes may help in the development of policies for at-risk populations in geographically defined areas. Future studies should focus on the identification of these vulnerable groups, in addition to elderly people and front-line healthcare workers, when determining prioritization in vaccination distribution plans.

Supplementary data
Supplementary data are available at *Transactions* online.

Authors' contributions: CL was responsible for investigation, supervision, validation, visualization, writing the original draft and reviewing and editing the manuscript. PMMB was responsible for data curation, formal analysis, methodology, software, writing the original draft and reviewing and editing the manuscript. MAF was responsible for conceptualization, data curation, validation, visualization, writing the original draft and reviewing and editing the manuscript. BSA was responsible for conceptualization, data curation, validation, visualization, writing the original draft and reviewing and editing the manuscript. BSA was responsible for conceptualization, data curation, validation, visualization, writing the original draft and reviewing and editing the manuscript. MAF was responsible for conceptualization, investigation, project administration, supervision, formal analysis, methodology, software, writing the original draft and reviewing and editing the manuscript. CL was responsible for conceptualization, investigation, supervision, validation, visualization, writing the original draft and reviewing and editing the manuscript.

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