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Spatial, spatio-temporal, and origin-destination flow analyses of patients with severe acute respiratory syndrome hospitalized for COVID-19 in Southeastern Brazil, 2020-2021

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ABSTRACT

Brazil experienced one of the fastest increasing numbers of coronavirus disease (COVID-19) cases worldwide. The Sao Paulo State (SPS) reported a high incidence, particularly in Sao Paulo municipality. This study aimed to identify clusters of incidence and mortality of hospitalized patients with severe acute respiratory syndrome for COVID-19 in the SPS, in 2020–2021, and describe the origin flow pattern of the cases. Cases and mortality risk area clusters were identified through different analyses (spatial clusters, spatio-temporal clusters, and spatial variation in temporal trends) by weighting areas. Ripley's K12-function verified the spatial dependence between the cases and infrastructure. There were 517,935 reported cases, with 152,128 cases resulting in death. Of the 470,441 patients hospitalized and residing in the SPS, 357,526 remained in the original municipality, while 112,915 did not. Cases and death clusters were identified in the Sao Paulo metropolitan region (SPMR) and Baixada Santista region in the first study period, and in the SPMR and the Campinas, Sao Jose do Rio Preto, Barretos, and Sorocaba municipalities during the second period. We highlight the priority areas for control and surveillance actions for COVID-19, which could lead to better outcomes in future outbreaks.

KEYWORDS: SARS-CoV-2 infection. Pandemics. Virus. SaTScan. Spatial analysis. COVID-19.

INTRODUCTION

With approximately 218 million confirmed cases and over 4.5 million deaths across 180 countries[1], severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the new coronavirus responsible for the coronavirus disease (COVID-19) pandemic, has changed the dynamics of human life[2]. The disease progresses to a severe form called severe acute respiratory syndrome (SARS) in 10-20% of patients. Individuals usually present with a fever, a dry cough, dyspnea/respiratory discomfort, and O_2 saturation < 95%[3].

SARS-CoV-2 caused more hospitalizations and deaths from SARS than any other causes, including influenza virus, other respiratory viruses or etiological agents, and unspecified causes, in 2020[3]. Furthermore, there were more SARS cases in 2020 and 2021 than in 2019[4].

In Brazil, the rapid spread of the virus triggered heterogeneous social and health repercussions in states and cities, resulting in the adoption of monitoring strategies to assist in the planning of social policies[5]. Currently, the Southeastern region of Brazil has the highest incidence of COVID-19 in the country, especially in the Sao Paulo State (SPS), which has recorded approximately 4.5 million cases and 157,000 deaths up to January 25th, 2022[4]. The first case of COVID-19 in Latin America was confirmed in the SPS, in a resident man who probably contracted the infection in Italy[6]. Knowledge of how the disease is distributed in a region allows us to understand how it spreads, how the cases are clustered, and how effective the installed care network is[7].

Spatial analysis methods and Geographic Information Systems (GIS) are used in public health systems to detect spatio-temporal clusters, which help in the planning and evaluation of healthcare services[8,9]. For instance, the SaTScan™ software (version 10.0.1, Kulldorff, Harvard Medical School, Boston, MA, USA), uses geographic coordinates to identify cases clustered in space and space-time[10].

Such methodologies are essential tools for identifying high-risk areas. They also support the implementation of control measures that aim to increase the efficiency of public resources, contribute to the visualization and crossing of information regarding socioeconomic, demographic, and environmental factors, and provide the opportunity to assess the geolocation of goods and services. This favors health surveillance as a whole[11]. Recently, GIS has played a key role in understanding the spatial clustering and transmission trends of COVID-19 in various parts of the world[2,12]. Based on spatio-temporal analyses performed in the SPS, it seems that the cases initially appeared in the São Paulo Metropolitan region (SPMR) and then progressed to the inland areas[13,14].

Therefore, we aimed to identify the spatial and spatio-temporal clusters of incidence and mortality rate among the patients hospitalized for SARS due to COVID-19 (SARS/COVID-19) in the SPS, Brazil, in 2020-2021. Additionally, we aimed to describe the origin flow pattern of the cases, and thus identify the municipalities with the highest instances of inter- and intra-state care, enabling more assertive public health measurements. This can facilitate the identification of crucial data to improve healthcare quality, enhancing the elaboration of situational diagnoses, and optimizing the guidance and feasibility of strategic actions to ameliorate the problem posed by COVID-19.

Ethical considerations

This study includes information on severe hospitalized cases and deaths from SARS/COVID-19 reported in the SPS, between the years 2020 and 2021. The confidentiality of information and anonymity of patients were guaranteed, and the data were used solely for the purpose of this study. The rules that regulate research on human beings, provided for in Resolution Nº 466, of December 12th, 2012, were considered; as well as compliance with the ethical specificities of research of strategic interest for the Brazilian Unified Health System (SUS), established in Resolution Nº 580, of March 22nd, 2018. Thus, this study was submitted to the Research Ethics Committee (reference) of the Sao Paulo State Health Department. The approval was granted through the Plataforma Brasil system, under reference Nº CAAE 56288622.3.0000.0086.

MATERIALS AND METHODS

This ecological study is focused on the SPS, Brazil, comprising 1,879 weighting areas (WA) and 17 regional health divisions (RHD). The SPS has an area of 248,219,481 km^2 and an estimated population of 46.6 million as of 2021[15,16]. Information regarding the date of symptom onset, sex, age, evolution, municipality of hospitalization/notification, and home address of each SARS/COVID-19 patient hospitalized between February 2020 and October 19th, 2021 was obtained by consulting the databases of the Influenza Epidemiological Surveillance System (SIVEP-Gripe) from the State's Epidemiological Surveillance Center.

To improve the accuracy of the analysis, we adapted the SARS/COVID-19 case definition by the Ministry of Health[17]. We only considered those cases in the SPS that were confirmed for SARS-CoV-2 infection using laboratory methods, such as real-time reverse transcription polymerase chain reaction (RT-PCR) or RT loop-mediated isothermal amplification (RT-LAMP) methods, and serological and rapid tests (antigens and antibodies). The cases confirmed by clinical examination, clinical imaging (computed tomography), or clinical-epidemiological assessment (close or home contact with a confirmed COVID-19 case) were excluded. During the spatial and spatio-temporal clusters analyses, we only considered the patients residing in the SPS and those with sufficient information (a home address) to perform geocoding.

Population information and cartographic materials (meshes of municipalities and WA) were obtained from the Brazilian Institute of Geography and Statistics (IBGE) and the SEADE Foundation[16,18,19]. As there were no population estimates per WA for 2020 and 2021, at the time of writing this paper, the population proportions were calculated using estimates from the 2010 demographic census. Infrastructure information regarding the rail, road, airport, and port units was obtained from the Ministry of Infrastructure[20].

The incidence (100,000 inhabitants) per epidemiological week was estimated according to the residential macro-region and RHD. We divided the study into two periods: the first from February 2020 to October 2020 and the second from November 2020 to October 19th, 2021. The homeless population (HP) cases were identified through dataset open fields regarding home address, using the terms "resident/situation," "area free/shelter/street/vulnerable," and "no fixed residence". These procedures were performed using the R program (version 4.1.0, R Core Team, Vienna, Austria).

Cases and deaths were geocoded from their home addresses based on the HERE API for QGIS (version 3.16, QGIS Development Team, Open-Source Software) with the Hqgis plugin (version 1.1.1, Klinger, QGIS Python Plugins Repository) from linear interpolation. We then exported the latitude/longitude coordinates and visualized them in QGIS to create a Kernel density estimation (KDE) map using the smallest radius of influence (9.0 km) from Ripley's K12-function analysis. It represents the limit and statistically significant distance considered as positive spatial dependence between the observation of the distribution of cases and the infrastructure[21], considering the coordinates of the cases and the public airport, port, rail, and road units.

Roads were divided, according to the study by Fortaleza *et al.*[22], into primary roadways (BR-050: Santos–Brasilia; BR-116: Fortaleza–Uruguay border) and secondary roadways (which have relevance in the SPS only). The coordinates of the railways and roadways were extracted at random points every 50 m using QGIS. Ripley's K12-function was executed in the R program using the Splancs package (version 2.01.42, Bivand, Repository CRAN) with 99 simulations. Subsequently, the infrastructure data were overlaid on the KDE map.

Database manipulations for spatial analysis were performed using R, and the data were de-duplicated based on the notification number. Using SaTScan™ software (version 10.0.1, Kulldorff, Harvard Medical School, Boston, MA, USA), the data were amassed into three tables containing IBGE's WA code as the means for linkage. The first table was used for incidence and mortality clusters, containing the number of cases and deaths, date of first symptoms, sex, and age range (0–19, 20–39, 40–59, 60–79, and ≥80 years). The second table was used for population statistics, containing WA population by sex, age range and year, and the third was used for centroid information, i.e., the latitude/longitude of the WA centroids. Using scanning statistics, the high-risk areas for the occurrence of SARS/COVID-19 were identified, and the relative risks (RR) were obtained.

Spatial clusters, space-time clusters, and analysis of spatial variations in temporal trends were performed using retrospective analysis and a discrete Poisson's model. We used the following conditions: circular-shaped clusters, secondary clusters with no geographic overlap, and adjustments based on age and sex. We applied Monte Carlo's method with 999 replications to estimate the probabilities and find the high-risk[10] areas of the significant clusters (p-value <5%).

During the spatial scan analysis, we also considered the Gini index, which is a measurement of statistical dispersion to obtain only the most likely clusters among the smaller clusters, instead of a single large cluster containing all the aforementioned ones[9]. The Gini index results for incidence and mortality were 10% and 50% in the analysis, respectively, in the first study period, and 2% for both in the second study period.

In the spatio-temporal scan and the analysis of spatial variation in the temporal trends, the maximum population size of each cluster was defined by the Gini index results of the spatial scan analysis for cases, deaths, and periods. We considered an aggregation time of one day, temporal trend adjustments for the day of the week, and a maximum reported cluster size within a 100 km radius. Subsequently, the SaTScan results were exported and combined with the WA map to produce thematic maps in the QGIS program.

Through the residence (origin of cases) and hospitalization/notification (destination of cases) data, a flow analysis was conducted using Flowmapper (version 0.4.1, Güllüoğlu, QGIS Python Plugins Repository) add-on in QGIS (version 2.18, QGIS Development Team, Open-source Software). It assessed the origin of the hospitalized patients from Brazilian states to the SPS municipalities and vice versa. Moreover, the files resulting from the flow analysis were transferred to the R program in a table with the distances (km) between the origin and destination centroids of hospitalizations to calculate the mean and median displacement of the hospitalized patients.

RESULTS

In total, 517,935 confirmed SARS/COVID-19 cases were reported in the SPS, considering all the criteria for confirmed cases, from February 2020 to October 2021. Of these, 152,128 (29.37%) patients had a fatal outcome. There were 4,816 (0.93%) SPS residents reported from outside the state. Among these, 4,106 cases were confirmed by laboratory methods and admitted to the SPS, and 837 had fatal outcomes (Supplementary Figure S1A).

Among the 513,119 reported cases residing in the SPS, 29,456 (5.74%) were confirmed using the following criteria: clinical examination, 3,729 (0.73%); clinical imaging, 20,631 (4.02%); and clinical-epidemiological assessment, 2,331 (0.45%). Among the 483,663 (94.26%) cases confirmed by the laboratory testing criteria, 388,920 (75.80%) were confirmed by molecular biology and 94,743 (18.46%) by other methods. Furthermore, among the 483,663 SPS resident cases confirmed by laboratory testing criteria, 142,573 (29.48%) patients died, while the remaining 471,680 (97.52%) were hospitalized. Among these hospitalized patients, 470,441 (99.74%) were hospitalized in the SPS (42,798 patients had no information on the municipality of hospitalization; hence, the municipalities of notification were considered) and 1,239 (0.26%) were hospitalized in other states (80 patients had no information on the municipality of hospitalization). Geocoding was possible in 94.53% of the laboratory-confirmed cases (457,222), and the remaining 5.47% (26,441) were excluded because they lacked proper address information (Supplementary Figure S1A and S1B).

The highest cumulative incidence was observed in the second period of the study, and the highest incidence was concentrated between March and July 2021, with variations in the RHD and macro-regions (Figure 1). The same trend was observed for mortality rates (Supplementary Figure S2).

The flow map represents the volume and origin of the 4,106 cases originating outside SPS but hospitalized in this state. The states of origin of the majority of cases admitted to the SPS were Minas Gerais (1,168, 28.45%), Mato Grosso do Sul (412, 10.03%), Mato Grosso (411, 10.01%), Para (308, 7.50%), Parana (294, 7.16%), and Amazonas (195, 4.75%); the remaining 1,302 cases (31.71%) were distributed among the other Brazilian states and the Federal District. Furthermore, 16 patients (0.39%) were from other countries (three from the Philippines, two from Argentina, two from Portugal, two from the USA, and one each from Bolivia, Mexico, Indonesia, India, Afghanistan, Spain, and Italy) (Figure 2A).

Regarding the destination of the 4,106 cases transferred to the SPS, the Sao Paulo municipality (SPM) received 2,325 (56.62%) of the cases from other states or countries, followed by the Sao Jose do Rio Preto (SJRP) (566, 13.78%), Barretos (131, 3.19%), Votuporanga (98, 2.39%), Ribeirao Preto (97, 2.36%), Bauru (71, 1.73%), Campinas (60, 1.46%), Franca (50, 1.22%) and Presidente Prudente (45, 1.10%) municipalities. The remaining 663 (16.15%) cases were distributed among the 119 municipalities.

Notably, 1,239 SPS residents were hospitalized in other Brazilian states. The states that received the most hospitalizations were Minas Gerais (297, 23.97%), followed by Parana (228, 18.40%), Rio de Janeiro (98, 7.91%), Bahia

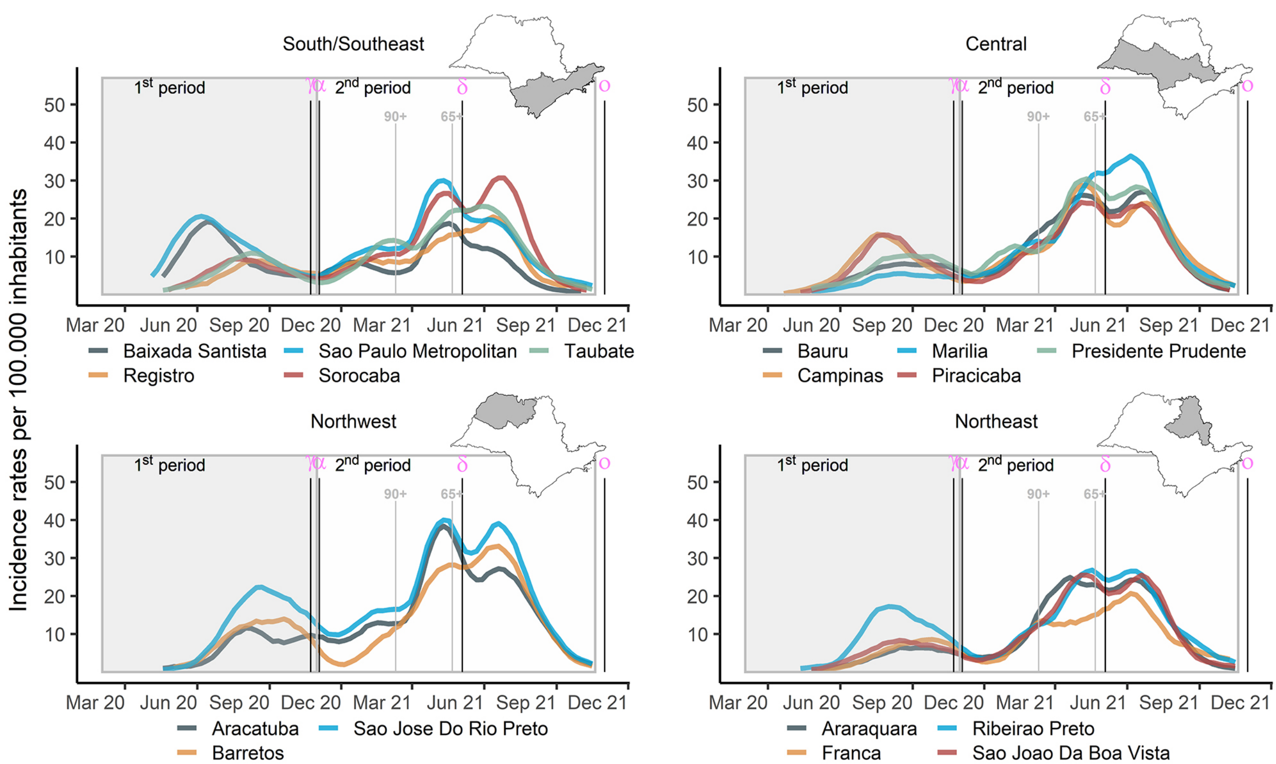

Figure 1 - Evolution of incidence rates per 100,000 inhabitants (moving average) of COVID-19 confirmed SARS cases by epidemiological week according to RHD, macro region and symptoms onset date, in the Sao Paulo State, Brazil. *1st period = symptom onset between February and October 2020; 2nd period = between November 2020 and October 2021. Variants emergence: Gamma (γ) and Alpha (α) in November 2020, Delta (δ) in May 2021, and Omicron (*O*) in November 2021. Start of vaccination campaigns according to age range, 90+ on February 8th, 2021; 65+ on April 21st, 2021.

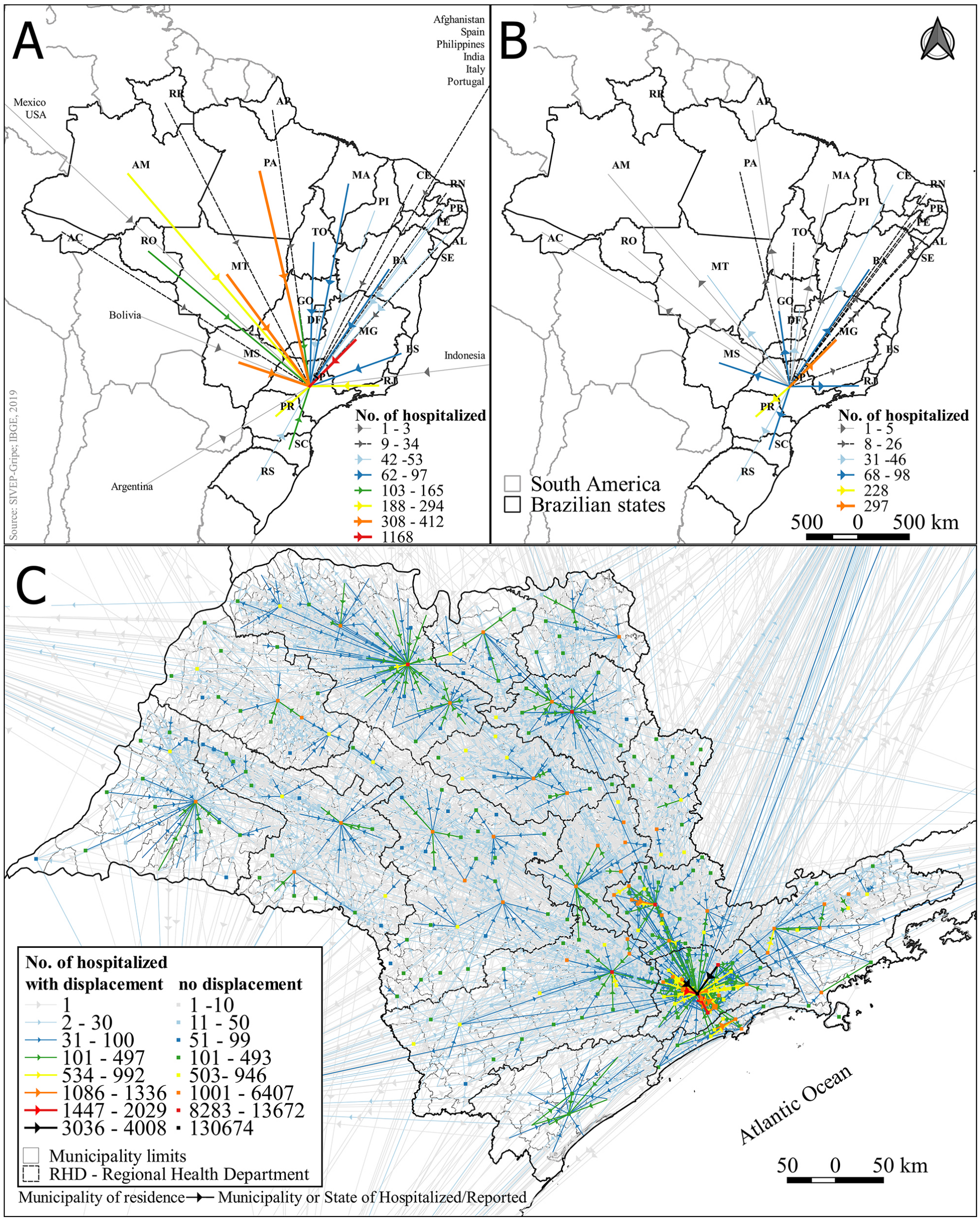

Figure 2 - Flow maps of SARS hospitalizations from COVID-19 destined for the Sao Paulo State, according to the state of origin (A), originating in the Sao Paulo State and destined for other Brazilian states (B), and map of internal flow of cases between municipalities in the Sao Paulo State and of cases with and without displacement* in municipalities (C), from February 2020 to October 2021. *without displacement = municipality of residence is the same as that of hospitalization.

(88, 7.10%), Mato Grosso do Sul (83, 6.70%), Goias (71, 5.73%), and Santa Catarina (68, 5.49%). The remaining 306 (24.70%) were distributed among the other Brazilian states and the Federal District, except for Roraima (Figure 2B).

Of the 470,441 patients hospitalized and residing in the SPS, 357,526 (76.00%) remained in the same municipality of origin and 112,915 (24.00%) were hospitalized in municipalities different from the original. Figure 2C shows the flow of cases (470,441 + 1,239) within the study area.

The municipalities that received most of the cases from other destinations are listed in Table 1. Overall, 283 municipalities received cases from other municipalities. Additionally, 24 states and the Federal District (112,195 + 1,239) received cases, with a mean and median distance between different cities of 44.4 km and 23.5 km, respectively, ranging from 4.4 km (with 78 patients between Poa and Ferraz de Vasconcelos municipalities) to 2,995.5 km (with two patients residing in the SPM and hospitalized in the state of Acre). It is worth mentioning the importance of the SPM during the study period. Not only did it receive the majority of cases but it also exported the greatest number of cases (8,013). Moreover, it had the most hospitalized cases without movement from the municipality of origin (hospitalized in and residents of the same municipality: 130,674 cases) (Figure 2C). Following the SPM, the places which exported the majority of cases were the Guarulhos (4,589), Osasco (3,961) and Santo Andre (3,166) municipalities; however, all the 645 municipalities reported exported cases.

On the Kernel map, there were 457,194 SARS/COVID-19 cases georeferenced by home address and infrastructure information, with 142,476 (31.17%) in the first period (Figure 3A) and 314,718 (68.84%) in the second (Figure 3B). It was observed that the hotspots overlapped with the main access roads, mainly close to international airports, railways, and areas of high population density.

Table 1 - The ten municipalities that received the most cases from other destinations in Sao Paulo State and the main donor of each municipality.

Receiver municipality	Cases	From municipalities	Main donor		
			Municipality	**cases**	**%**
Sao Paulo	29,125	339	Guarulhos	4,008	13.76
			Osasco	3,036	10.42
			Taboao da Serra	1,447	4.97
			Sao Bernardo do Campo	1,253	4.30
			Santo Andre	1,218	4.18
			Carapicuiba	1,143	3.92
			Diadema	1,086	3.73
Sao Bernardo do Campo	6,471	92	Sao Paulo	2,029	31.36
			Diadema	1,190	18.39
			Santo Andre	1,182	18.27
			Maua	489	7.56
Sao Jose do Rio Preto	6,375	194	Mirassol	776	12.17
			Jose Bonifacio	361	5.66
			Bady Bassitt	346	5.43
			Guapiacu	335	5.25
Campinas	4,462	130	Sumare	1,095	24.54
			Hortolandia	916	20.53
			Paulinia	446	10.00
Santos	3,043	45	Sao Vicente	1,336	43.90
			Praia Grande	565	18.57
			Cubatao	319	10.48
			Guaruja	309	10.15
Sao Caetano do Sul	2,656	51	Sao Paulo	1,212	45.63
			Santo Andre	579	21.80
			Sao Bernardo do Campo	475	17.88
Santo Andre	2,638	54	Sao Paulo	958	36.32
			Sao Bernardo do Campo	688	26.08
			Maua	400	15.16
Osasco	2,627	106	Sao Paulo	720	27.41
			Carapicuiba	534	20.33
			Barueri	229	8.72
Ribeirao Preto	2,611	125	Jardinopolis	291	11.15
			Sertaozinho	263	10.07
Jundiai	2,432	77	Varzea Paulista	662	27.22
			Campo Limpo Paulista	370	15.21
			Itupeva	235	9.66

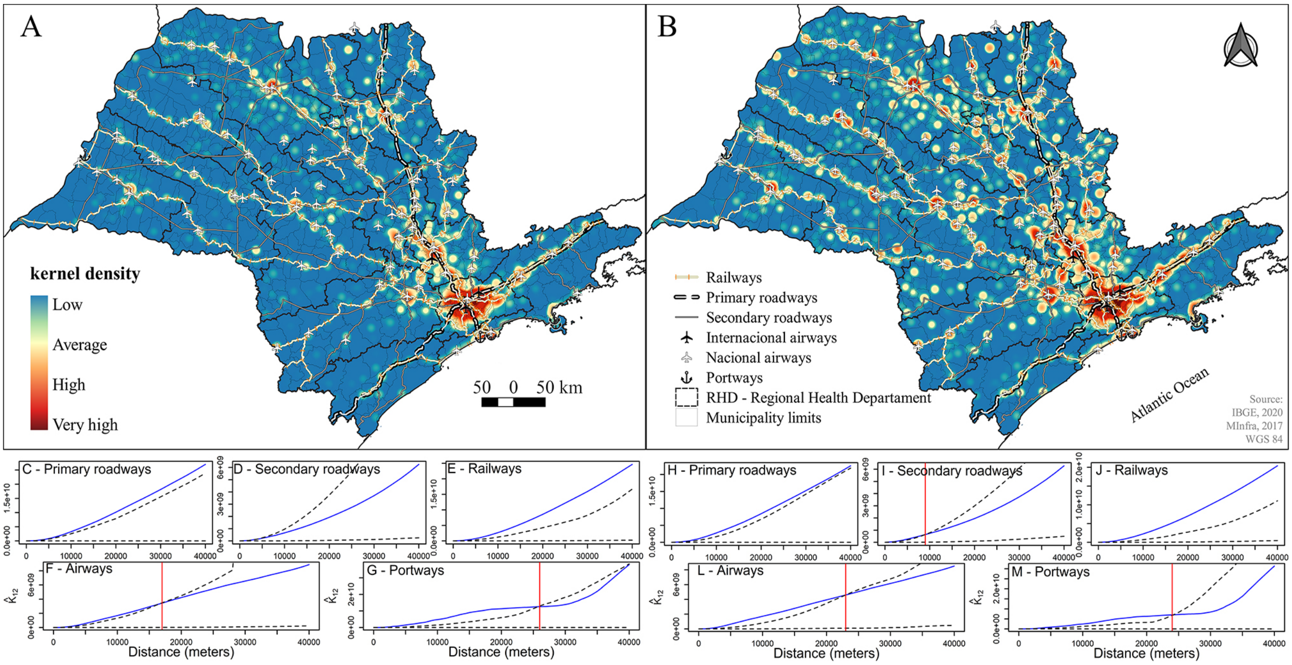

Figure 3 - Kernel density maps (9 km radius of influence) of SARS cases and deaths by COVID-19 and infrastructure data for the Sao Paulo State, Brazil, in the 1st period – between February 2020 and October 2020 (A); and 2nd period – from November 2020 to October 2021 (B). Graphs of the analysis of the bivariate Ripley's K12-function between cases and infrastructure (primary and secondary roads, railways, public airports and ports) for the 1st period (C-G) and 2nd study period (H-M). The blue curve that continues above the envelope shows a positive spatial dependence between cases and infrastructure, and the red line shows the boundary of spatial dependence.

Ripley's K12-function indicates the existence of positive spatial dependence between the cases and the primary roadways and railways, both in the first and second study periods (Figures 3C, 3E, 3H, and 3J). Regarding secondary roads, in the first period, the distribution indicated that it was random in terms of space, while in the second period, spatial dependence (up to 9 km) was observed (Figures 3D and 3I). The analysis between the cases and the public airport and port locations in the region during both periods indicates positive spatial dependencies up to a distance of 17-26 km (Figures 3F, 3G, 3L, and 3M).

In the spatial analysis of the first study period, 12 significant clusters of SARS/COVID-19 cases were identified, mainly in the SJRP and SPMR RHD. The clusters with the highest RR and greatest territorial extensions were found in the center of the SPM (RR of cluster 1-RR1 = 1.70), followed by another cluster that encompassed the SJRP, Bady Bassitt, Mirassol and Balsamo municipalities (RR4 = 1.74). Furthermore, clusters were found in other regions of the SPMR RHD, such as the Campinas, Ribeirao Preto, Caraguatatuba, Porto Feliz, Piracicaba, and Sumare municipalities, and in the Baixada Santista RHD. Three clusters with a high mortality risk due to SARS/COVID-19 were identified in the SPMR RHD (RR1 = 1.91), and in the SJRP (RR2 = 1.81) and Ribeirao Preto municipalities (RR3 = 1 .68) (Figure 4A and 4B, Supplementary Table S1).

In the space-time analysis of the first study period, 14 clusters with a high risk for the occurrence of significant SARS/COVID-19 cases were identified. The first cluster was identified in the period between March 19th, 2020 and August 1st, 2020 in the SPMR RHD, the western part of the SPM, and the Guarulhos and Sao Caetano municipalities (RR1 = 2.68). It was also the cluster of a longer duration. This was followed by three clusters starting in April 2020 in the central region of the SPM (Cluster 2), the western region of the SPMR and the Baixada Santista RHD (Cluster 3), and the northern region of the SPMR and the Campinas RHD (Cluster 4).

Subsequently, nine clusters appeared, starting between May and June 2020, with the highest RR in the RHD of Marilia (RR14 = 3.70), Bauru (RR12 = 2.47), SJRP, Barretos, Franca, Araraquara, and Ribeirao Preto (RR5 = 2.12) municipalities. Moreover, six other clusters were observed in the RHD of the Presidente Prudente (Cluster 9), Campinas, Piracicaba (Cluster 6), Bauru (Cluster 8), SJRP, Aracatuba (Cluster 7), Taubate (Cluster 10), Registro and Sorocaba (Cluster 11) municipalities. The first period ended with a smaller cluster starting in August in the Andradina municipality (Cluster 13). Furthermore, six clusters with a high mortality risk were identified, which overlapped with the clusters of incidences in the RHD of the SPMR and Baixada Santista region (Cluster 1), and of the

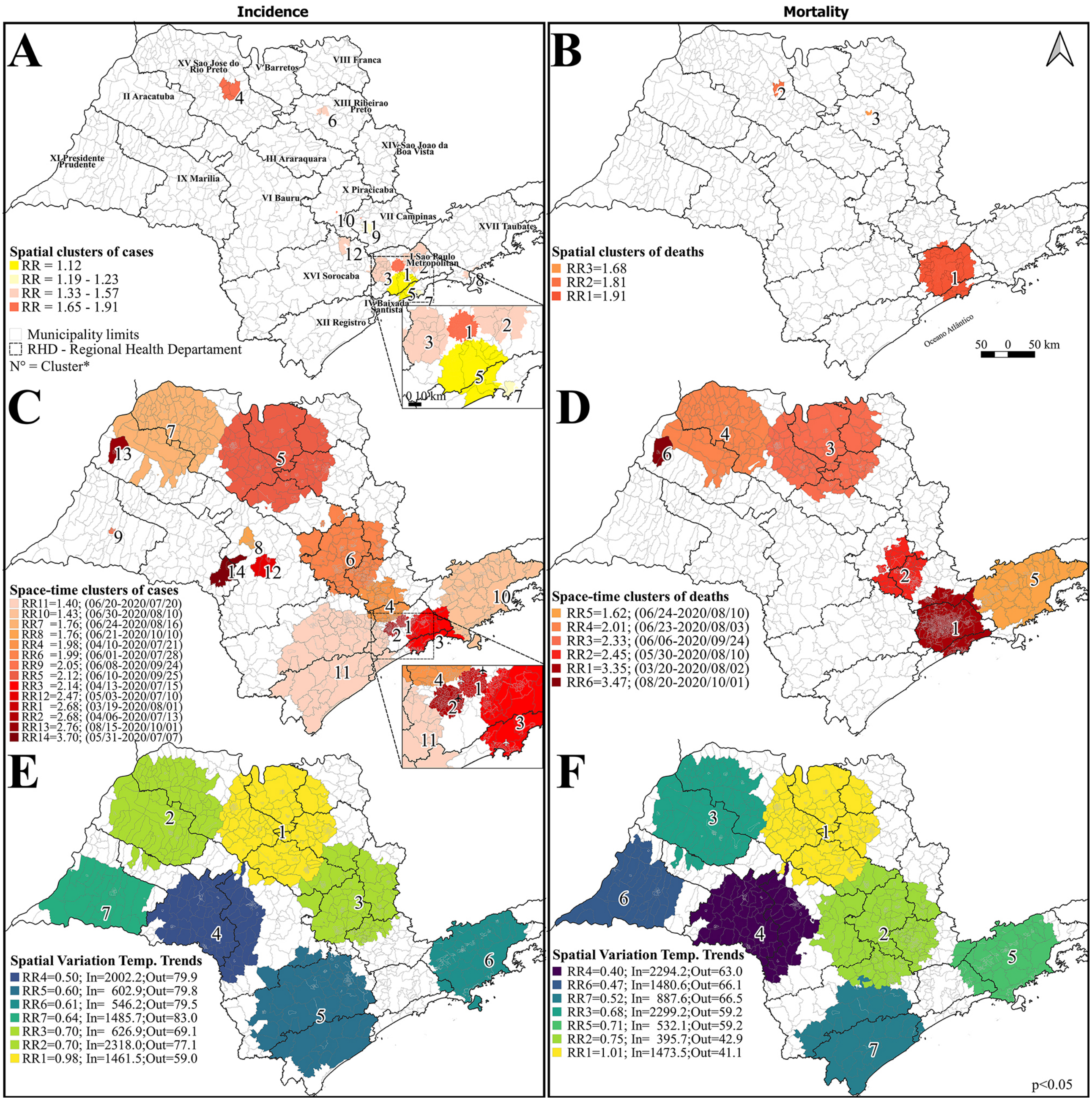

Figure 4 - Maps with spatial clusters (A, B), spatio-temporal clusters (C, D) and spatial variation in temporal trends (E, F) for SARS cases (A, C, E) and deaths (B, D, F) by COVID-19, according to weighting areas in the Sao Paulo State, Brazil, in the first study period – from February to October 2020. *Codes of the numbers of clusters in Tables S1-S3. RRnº = relative risks of the cluster with same Nº. In = internal time trend and Out = external time trend to the cluster.

Campinas and Piracicaba (Cluster 2), Barretos and Ribeirao Preto (Cluster 3), SJRP (Cluster 4), Taubate (Cluster 5) and Aracatuba (Cluster 6) municipalities (Figure 4C and 4D, Supplementary Table S2).

Seven significant clusters were identified in the analysis of spatial variation in temporal trends of the first period. The values of internal time trends of annual increase in cases varied from 546.2% to 2,318.0% and external trends from 59.0% to 83.0%. The cluster with the highest internal tendency to increase (2,318.0%) occurred in the RHD of SJRP and Aracatuba municipalities. Furthermore, seven clusters with fatal outcomes were identified in this analysis, following a trend similar to that of the cases (Figure 4E and 4F, Supplementary Table S3).

In the second period, 49 and 34 spatial clusters at a high risk of incidence and mortality were identified, respectively, and these were distributed throughout the state (Figure 5A and 5B). The clusters of cases with the highest RR were found in the center of the SJRP RHD (RR1 = 2.06), the western region of the SPM (RR20 = 2.02), the Barueri and Santana do Parnaiba municipalities (RR5 = 2.04) municipalities, the Taubate RHD, the Caraguatatuba municipality (RR13 = 1.90), the Araraquara municipality (RR34 = 1.88), the Bauru RHD (Lencois Paulista municipality) (RR17 = 1.83), the Presidente Prudente municipality (RR12 = 1.63), the Sorocaba RHD, and the Salto de Pirapora, Sorocaba, and Votorantim municipalities (RR2 = 1.58) (Figure 5A, Supplementary Table S1).

The clusters with the highest RR for mortality were found in the SJRPM (RR1 = 1.89), the Sorocaba RHD (RR4 = 1.85) and the Barueri (RR9 = 1.78) and Caraguatatuba (RR18 = 1.72) municipalities. The results of the mortality outcomes maintained the pattern shown by the clusters of incidences; however, in the SPM, clusters with a high risk of mortality were found at the peri-urban

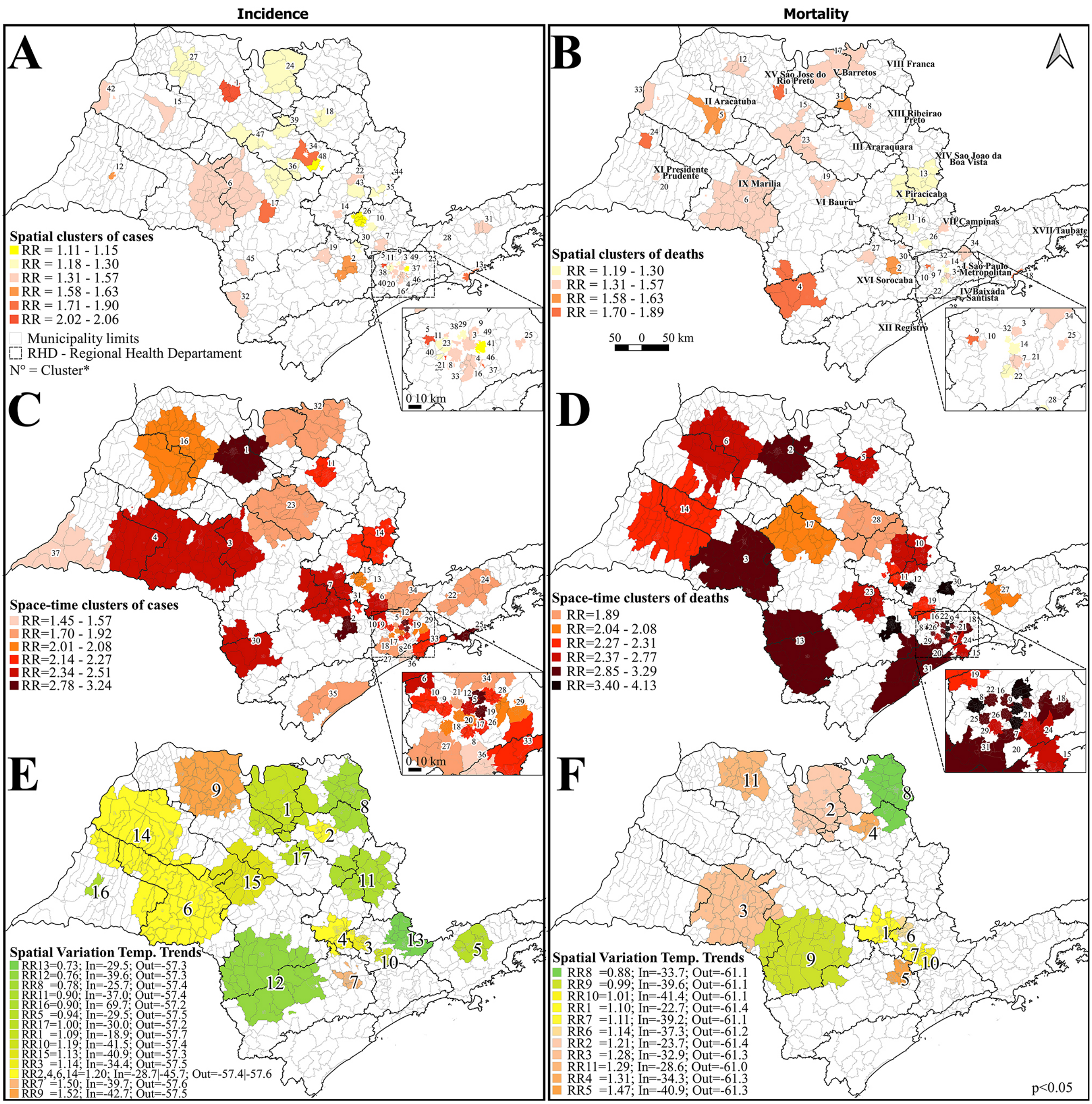

Figure 5 - Maps with spatial clusters (A, B), spatio-temporal clusters (C, D) and spatial variation in temporal trends (E, F) for SARS cases (A, C, E) and deaths (B, D, F) by COVID-19, according to weighting areas in the Sao Paulo State, Brazil, in the second study period – from November 2020 to October 2021. *Codes of the numbers of clusters in Table S1-S3. RRnº = relative risks of the cluster with same Nº. In = internal time trend and Out = external time trend to the cluster.

area and in the municipalities surrounding it (Figure 5B).

In the second study period, the space-time analysis identified 37 high-risk case clusters, of which 31 started between December 2020 and February 2021. Among these, the highest RR were reported in municipalities belonging to the SJRP RHD, such as Barretos (RR1 = 3.24), Sorocaba (RR2 = 3.11), and Guarulhos (RR12 = 2.93), in the eastern region of the SPM (RR19 = 2.89), and in the Caraguatatuba municipality (RR25 = 2.78). In addition to five more clusters starting in March 2021, and one in May 2021, in the RHD of Registro (Cluster 35), Taubate (Cluster 24) and Franca (Cluster 32) municipalities, there were two clusters in the Baixada Santista region (Cluster 33 and 36) and the Presidente Prudente municipality (Cluster 37). There were 31 high-risk mortality clusters identified across the state, of which 28 started in January/February 2021 and three in March 2021. Those with the highest RR were found in the RHD of Campinas (RR12 = 3.60 and RR30 = 4.13) and Sorocaba (RR1 = 3.47) municipalities, and in the SPM (RR9=3.40) and the municipalities around it (RR4 = 4.06, RR8 = 3.86, and RR7 = 3.73) (Figure 5C and 5D, Supplementary Table S2).

In the analysis considering the spatial variation in temporal trends during the second study period, 17 significant clusters were identified. Unlike the clusters of the first study period, the trend of the cases showed an annual percentage decrease, with the internal trend varying from −45.7% to −18.9% and the external trend from −57.7% to −57.2%. However, the cluster located in the Presidente Prudente RHD (in the Santo Anastacio municipality) (Cluster 16) was an exception, with an internal trend of 69.7% of annual increase and an external trend of –57.2% of annual decrease in the cases. In the mortality analysis, 11 clusters were identified, all of which presented an internal and external trend of an annual percentage decrease (Figure 5E and 5F, Supplementary Table S3).

DISCUSSION

The analysis of spatial and spatio-temporal clusters, using the data from February 2020 to October 2021, showed that the virus progression did not occur randomly or uniformly throughout the space, but rather due to specific social behaviors among the population. Although there are several methods that analyze the global and local clusters[23,24], we chose the scanning method to identify high concentration areas of cases and deaths. This showed that the location of high-risk areas in the SPS was highly dynamic throughout the pandemic months, with the cases starting in the SPMR and moving inland, which supports the findings of other studies[22,25].

Regarding the hospitalization flow, there was a large patient influx from other states into the SPS, notwithstanding that a large number of patients from the SPS were hospitalized in the SPMR and SJRPM. These regions are SPS's economic hubs and contain large care infrastructures, which can probably sustain the demands of neighboring areas because they contain health equipment of a greater resolution[14].

This effect could also be seen on the Kernel map, which showed the formation of spatial clusters in the largest and most populous municipalities in each region. This corroborates the findings of Alcântara *et al.*[13] which denote a spatial dependence in places with a higher population density.

Among the hospitalizations, the SPM received the most patients from the SPS as well as from other states. Despite having exported some patients, the balance was still positive, and it received more patients for hospitalization. These flow dynamics in a metropolitan region were also observed in Rio de Janeiro[26]. In other words, efforts to face the pandemic (vaccination and social distancing, in addition to other non-pharmacological measures) cannot be isolated in a municipality. Furthermore, considering the logic of the healthcare network, vaccination coverage must be uniform in the whole region[26] for the SPS and other states to avoid over-occupation of hospital beds.

A relationship was observed between the presence of airports, ports, railways, and primary highways and case concentration, thus confirming the role of human mobility in the spread of the virus. Similar results have been reported by Rex *et al.*[25] Secondary roads did not influence the concentration of cases in space during the first study period. The initial virus control strategies within the state only allowed the operation of essential services. This probably influenced the spread of the virus since it followed the main supplies' distribution routes[22]. Fortaleza *et al.*[22] demonstrated that the dispersion of SARS-CoV-2 occurs by spatial contiguity, with an initial introduction in capital cities and then moving toward the nearest municipalities. It is also possible that it dispersed over long distances through major highways and airways and then moved to less populated areas. This may have occurred during the second period, when the secondary roads had a positive spatial relationship between the cases.

Kraemer *et al.*[27] found that the spatial distribution of COVID-19 cases was well explained by human mobility data at the beginning of the pandemic. However, after the implementation of control and distancing measures, the relationship dwindled along with the growth rates of cases in most locations[27]. This phenomenon was more evident in the first period of our study, where the first high-risk clusters were located in the SPMR and Baixada Santista region, both in the spatial and spatio-temporal analyses, and presented high RRs. The first case of COVID-19 in Brazil was detected in the SPM, in the SPMR[6].

The SPM followed by the Guarulhos municipality were the regions with the most imported hospital admissions. The latter contains the Sao Paulo/Guarulhos International Airport, the largest airport in Brazil, with routes to 103 destinations in 30 countries. It not only connects the main cities in Latin America but also has direct flights to North America, Europe, Africa, and the Middle East[6]. The Baixada Santista region is where the Port of Santos, the largest in Latin America, is located. This port offers support for both cargo and passenger ships. In 2018, the port hosted ships with more than 20 countries as the origin or destination and provided transport for 255,964 passengers[28].

The incidence and mortality rates for all the SPS RHD were higher in the second study period than in the first study period. In the second period, a new pattern of spatial dispersion was observed, where high-risk clusters were spread throughout the state and not restricted to capital cities and the most populous municipalities. This may be a reflection of the greater flexibility in the control measures[29,30], agglomerations promoted during the pre-election and election times in November, trips and celebrations during the holiday season, and the opening of schools in January 2021[14,31,32].

It is important to mention that each municipality in the state dealt with the restrictive measures independently, which may have led to different epidemiological scenarios throughout the state. For instance, Araraquara municipality showed a large increase in the number of cases and deaths in the initial months of 2021 but later imposed more restrictive control and isolation measures (from February to March 2021)[33]. Additionally, new variants of SARS-CoV-2 were in circulation in the SPS in the second study period, namely the Alpha and Gamma variants from November 2020 and the Delta variant from May 2021. This may have influenced the increase in the number of cases and high transmission rate in the population.

In the space-time scan analysis, we observed a large number of clusters, denoting that all regions of the state were affected at some point during the pandemic. The main cases and death clusters, which had greater extension in the first period, occurred between March and August 2020 in the SPMR and Baixada Santista region. In the second period, the main clusters of cases and deaths occurred between February and June 2021 in the SPMR, the Campinas, SJRP, Barretos municipalities, and the Sorocaba RHD.

Regarding the spatial variation in temporal trends, there was an overall decrease in both cases and deaths across the state from the second half of 2021. This reduction was probably a consequence of the mass vaccination campaign, which prioritized those with the highest mortality risk, such as the elderly and healthcare professionals. Nevertheless, several other factors may be associated with the spatio-temporal inequality of cases and deaths, such as the prevalence of comorbidities in the population and risky behaviors, such as smoking and alcohol consumption[14].

However, this decrease in the number of cases should be interpreted cautiously, since one region, Presidente Prudente, showed an increasing trend. This one-off trend of increase could be because the SPS started to ease the restrictions in August 2021, as defined by the Government of Sao Paulo[30], which may have also caused a subsequent increase in cases in other regions. Moreover, the new variant Omicron, confirmed by the National Health Surveillance Agency (Anvisa) in the SPS in November 2021, may further influence the dynamics of the disease in the future. It was reported in two patients who disembarked at Guarulhos[34,35]. Comparison of the data on genetic mutations of variants prior to Omicron suggests that vaccines are still effective, the disease is less severe at population level, the risk of hospital admissions decreases with the booster-dose vaccine, and RT-PCR diagnostics continue to be effective in detecting the infection. However, evidence has shown that the Omicron variant is more infectious and transmissible than the previous variants[35,36].

Among the limitations of this study, the analysis of only severe cases and deaths due to COVID-19 is an obvious one. However, the data reflect hospitalizations, deaths, and, in part, the main origin-destination flow during the critical months of the pandemic in Brazil. Another limitation is the possible underreporting of the HP cases, since the notification form does not have a specific field for this information, in addition to the lack of public policies for this population, such as access to laboratory tests[37,38] and social distancing measures. Notably, the number of HP cases has been increasing during the last few years[39] and may have increased further during the pandemic[38].

This study has several strengths. A significant proportion of cases and deaths were geocoded (94.53%); thus, the analyzed data have great precision of information. It considers the home address (WA) to understand the epidemiological patterns in each municipality, even considering that the disease does not respect municipal limits[40]. Furthermore, for a more detailed analysis, we only used cases confirmed by laboratory tests, accounting for 94.19% of the SPS total cases reported and 94.26% of the SPS residents.

The ecological design made it possible to highlight nondetectable effects at an individual level, and the choice of strict spatial variation in space-time allowed the detection of geographic clusters with a high risk of COVID-19 in the SPS.

The use of spatial analysis tools aids our understanding of the behavior of SARS-CoV-2 in populations, considering their space occupation and mobility. These techniques also contribute to the detection of locations at a high risk of aggravation or mortality from the disease, which can help prioritize policies and mitigation actions by the responsible bodies. Our results provide valuable information for the precise identification of places where local transmission clusters may first emerge, which is critical for the better coordination of response actions.

CONCLUSIONS

The locations of the high-risk areas for SARS/COVID-19 in the SPS were highly dynamic during the pandemic months, starting at the SPMR and moving inland to other municipalities within the state. A relationship was observed between the presence of airports and ports and the concentration of cases, confirming the role of human mobility in the spread of the virus. Notably, the incidence, mortality rates, and presence of high-risk clusters were higher in the second study period than in the first period throughout the SPS RHD. Starting in the second half of 2021, there was an overall decrease in the number of both cases and deaths across the state. However, this decrease should be interpreted cautiously. The emergence of a new variant may also lead to a subsequent increase in the number of cases. This study highlights priority areas for control and surveillance actions for COVID-19 and other viruses with a similar spread mechanism.

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AUTHORS' CONTRIBUTIONS

RGSP, CL, PMF, TRMPC: conceptualization; RGSP, CL, PCCL, LN, ETM, CMT, PCMM, ALC: data curation; RGSP, CL, PCCL, PMF, ETM, LN, CMT, ACGP: methodology; RGSP, PMF, LN, ACGP: formal analysis; RGSP, CL: writing – original draft; RGSP, CL, PCCL, LN, ETM, CMT, ALC, PCMM, CSS, PMF, ACGP, ALFY, TRMPC: investigation, writing (reviewing and editing), and visual aspects; ALFY, TRMPC: supervision.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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