doi:10.20944/preprints202204.0010.v1

*Article*

# Identifying Hotspots of peoples diagnosed with tuberculosis and drug addiction of alcohol, tobacco and other drugs through a geospatial intelligence application on communities from Southern Brazil

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**Abstract:** (1) Background: tuberculosis (TB) is considered one of the leading causes of death by a single infectious agent worldwide. This study aimed to identify hotspots of people diagnosed with tuberculosis and abusive use of alcohol, tobacco and other drugs in communities through a geo-spatial intelligence application; (2) Methods: ecological study with a spatio-temporal approach. We considered tuberculosis cases diagnosed and registered in the Notifiable Diseases Information System, which presented information on alcoholism, smoking, and other drugs. Spatial Variations in Temporal Trends (SVTT) and scan statistics were applied for the identification of Hotspots; (3) Results: of 29.499 cases of tuberculosis were identified. And when we applied the STTT for alcoholism, three Hotspots were detected, one of which was protective (RR: 0.08 – CI95%: 0.02 – 0.32) and two at risk (RR:1.42 – CI95%: 1.11 – 1.73; RR: 1.39 - CI95%: 1.28 – 1.50). Regarding smoking, two risk clusters were identified (RR: 1.15 - CI95%: 1.01 – 1.30; RR: 1.68 - CI95%: 1.54 – 1.83). For other drugs, a risk cluster was found (RR: 1.13 - CI95%: 0.99 – 1.29) and two protections (RR: 0.70 - CI95%: 0.63 – 0.77; RR: 0.76 – CI95%: 0.65 – 0.89); (4) Conclusions: it was evidenced in the communities a problem of TB and drug addiction. Use disorder perhaps in a person's brain and behavior and leads to an inability to continue their treatment, putting the community at risk for TB.

**Keywords:** Tuberculosis 1; Alcoholism 2; Illicit drugs 3; Tobacco use disorder 4; Spatial analysis 5

## 1. Introduction

Tuberculosis (TB) is considered one of the leading causes of death by a single infectious agent worldwide. It is one of the leading causes of preventable death that persists across the population[1-3]. Brazil is one of the countries with the highest number of TB cases, since 2003 ranking the 16th position among the 22 countries with the highest TB cases in the world. These countries are responsible for a global burden of the disease of 80% nearly[2-4].

In 2020, Brazil presented an incidence of 31.6 cases per 100,000 inhabitants[3]. It is noteworthy that many factors influence the maintenance of the disease in the country, such as social inequalities that significantly increase the burden of the disease and lead to unfavorable outcomes, such as treatment dropout, hospitalizations, drug-resistant TB (DR-TB), and death[5,6].

TB affects mainly vulnerable populations mainly those with mental health disorders and substance use disorders, such as alcohol use, tobacco, and other drugs [7,8]. A study conducted in South Africa showed an estimated 10.4 million new cases of TB, of which 4.7% were related to harmful alcohol use[9]. Thus, the use of alcohol, tobacco, and other drugs are aspects that should be considered in the elaboration of measures and strategies aimed at the elimination of TB [8].

Studies [1,7-10] suggested an association between use of alcohol, tobacco, and other drugs with latent infection among people who make chronic use of these substances. Those people have greater odds for the development of active TB, treatment failures related to therapeutic interruptions and/or discontinuities, and early deaths, mainly in the male population.

Although the association between TB and alcohol, tobacco, and other drugs is a priority issue to design health policies addressed to eliminate the disease, it is still few explored in the scientific literature from the perspective of vulnerable population and hazard-prone territories.

In Brazil, although each territory is under accountability of a health service and health workers, most of them do not have appropriate technologies for stratifying the risk that their community is exposed, which makes the geospatial intelligence an important allied. Therefore, the study aimed to identify Hotspots of peoples diagnosed with tuberculosis and abusive use of alcohol, tobacco and other drugs on communities through a geospatial intelligence application in Southern Brazil.

## 2. Materials and Methods

**Study design and location:**

Ecological study, conducted in the state of Paraná, located in the South of Brazil macro-region and located in the geographical coordinates 24º59' S latitude and 53º56' W longitude, with an estimated population of 11.34 million inhabitants, with the fifteenth state having the largest national territory and the fifth for the population[5].

For the study, we used as a unit of geographical analysis the 399 municipalities that make up the state of Paraná, which is subdivided into 22 regional health and nine mesoregional municipalities, being: West, Northwest, Western Center, Central North, Pioneer North, Eastern Center, Metropolitan of Curitiba, Southeast, Center-South, and Southwest. Figure 1 illustrates the location of the state and its mesoregions.

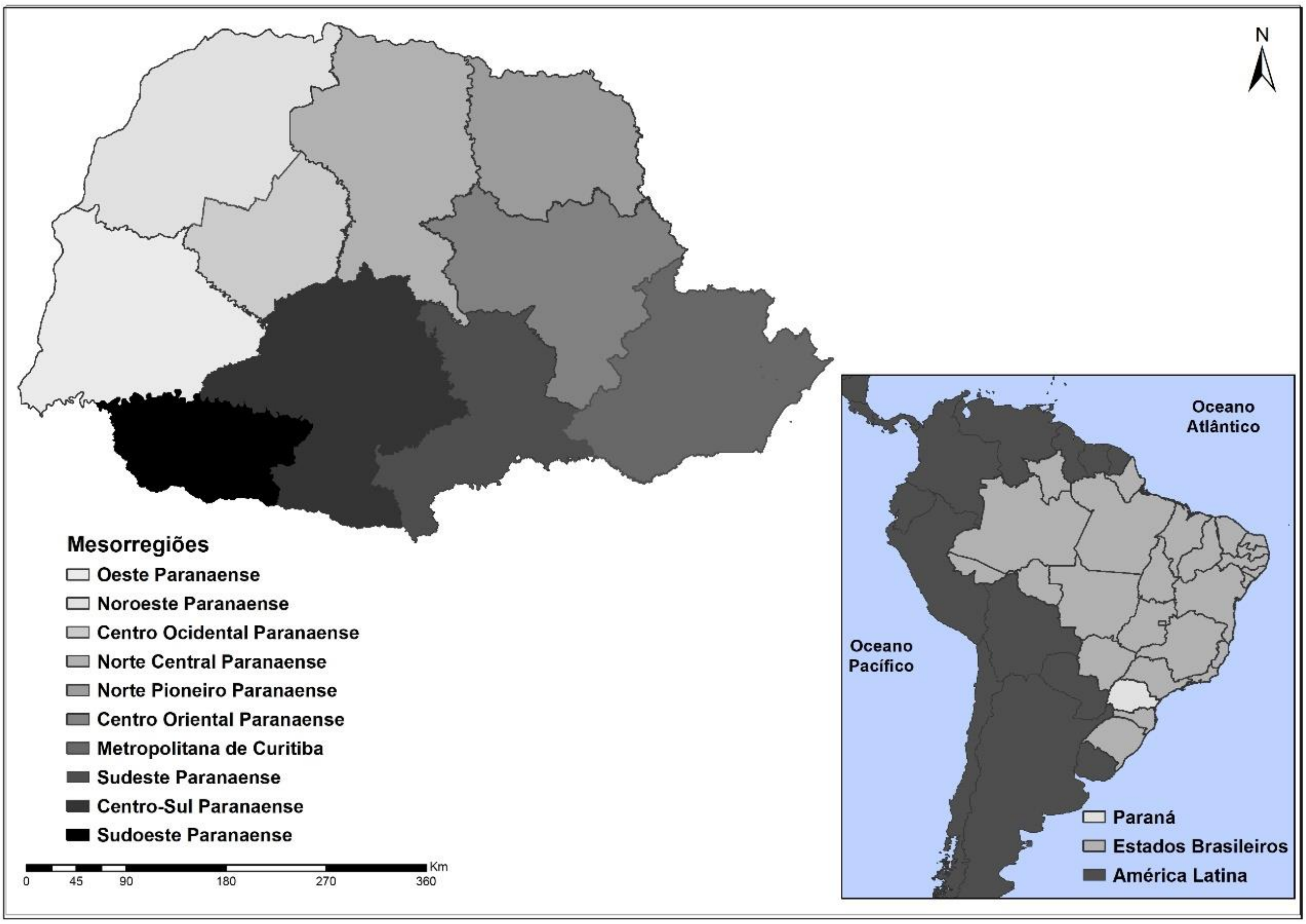


**Figure 1.** Geographic location of the state of Paraná and its mesoregions.

**Population, source of information, and study variables**

The study used secondary data from TB notifications registered in the Information System of Notifiable Diseases (SINAN), of the Secretariat of Health of Paraná, from 2008 to 2018, and these data were made available by the Secretary of State for Health (SESA) in Excel file, on May 11, 2020.

We considered as the study population confirmed cases of TB and reported use of alcohol, tobacco, and other drugs. The cases that did not have in their notification the use of alcohol, tobacco, and other drugs and missing data were excluded.

We used the following variables available in SINAN: Sex: (male and female); Age group: (< 15 years, 15 to 29 years, 30 to 59 years and > 60 years); Race: (white, black, yellow, brown and indigenous); Schooling: (illiterate, up to eight years of study and more than eight years of study); Type of case: (new case, recurrence, reinstatement after dropout, and transfer); Classification: (pulmonary, extrapulmonary, and pulmonary + extrapulmonary); Drug sensitivity testing (resistant only to isoniazid, resistant to rifampicin, resistant to isoniazid and rifampicin, resistant to other drugs of 1st line, and sensitive); Outcome of the treatment (cure, abandonment, death from TB, death from other causes, and DR-TB).

**Data analysis**

Initially, descriptive statistics were applied to calculate absolute and relative frequency measurements for categorical variables, using the software Statistica (12.0). The TB incidence rate per 100.000 inhabitants (I) was calculated by dividing the number of new cases in the study ($Y_i$) by the urban population of the state in 2010 ( $P_i$) before each municipality, and finally multiplying by 1/10, referring to the years under study, according to the formula below (GORDIS, 2009):

$$I = \frac{Y_i}{P_i} \times \frac{1}{T}(100.000)$$

To identify Hotspots, the geographic coordinates of each municipality were first obtained from the free-access Google Earth tool. Then the case georeferencing technique was performed in the ArcGIS software, version 10.5.

Then, for the detection of clusters of spatial risk for the occurrence of TB, concomitant to the use of alcohol, tobacco, and other drugs, we used the Purely Spatial Scan Statistics (EVPP), developed by Kulldorff and Nagarwalla (1995)[12], and used the Satscan software (version 9.6).

The scanning statistic consists of the formation of circles that move throughout the area under study, that is, the state of Paraná, around the centroids, which correspond to the center of each municipality under analysis, that is, a centralization process is performed, the radius of which may vary from zero to the limit determined by the researcher[13].

The identification of Hotspots was performed by calculating the number of events found within each circle. If the observed value was higher than expected in the region z, delimited by the circle, was called agglomerated. Otherwise, the radius of the circle was enlarged to a new centroid, and so it occurred until all centroids were tested under the following hypotheses: $H_0$: no agglomeration in the study region and $H_1$: the region z is a cluster[14], so that cluster was understood to be the region with greater or lower risk of having TB and using alcohol, tobacco or other drugs when compared to other regions.

The Likelihood Function calculated to define Hotspots has been maximized in general in the checked windows, the maximum log-likelihood ratio (Likelihood Function - LLR) corresponds to the most likely cluster, which means it is the least likely to have occurred at random; meanwhile, other statistically significant ordinal LLRs have been combined with secondary clusters.

The P-value of the maximum likelihood test was obtained through Monte Carlo hypothesis tests and randomly replicated simulation tests to compare the maximum LLR classification of real data with random data.

The Hotspot's relative risk (RR) was defined with the risk within the scan window compared to the risk outside the scan window, representing how much more common the disease is in a given location and time period than the baseline[15]. RR equal to 1 means no statistically significant difference between exposed and unexposed groups; if RR <1 is equivalent to low risk (or protection), RR> 1 can be understood as an area of risk.

The following criteria were used to identify Hotspot: Poisson Discrete Model, non-overlapping geographic clusters, maximum cluster size equal to 50% of the exposed population, agglomerates with a circular shape, and 999 replications following the Monte Carlo criteria.

After the identification of purely spatial Hotspot[16] and temporal space, to assess the reliability of RR values, the respective 95% confidence intervals (95%CI) were calculated. Thematic maps were developed using ArcGIS software (version 10.6).

Then, the Spatial Variation in Temporal Trends (SVTT) technique was used to detect and infer risk Hotspots with significantly different time trends. In this analysis, the scan window is purely spatial in nature[16]. However, the time trend is calculated inside and outside the scan window for each location and size.

When a difference in temporal trend between internal and external areas is detected, its statistical significance is calculated[17]. The following hypotheses were tested in each window: $H_0$: the time trends are the same in all areas, and $H_1$: the trends are different. Thus, risk clusters indicate areas with a statistically different temporal trend from the temporal trend outside these clusters (considering a type I error of 5%).

The results indicate an Internal Temporal Trend (TTI), which consists of the degree of growth or decrease of the event within the cluster of risk, and an External Temporal Trend (TTE), which corresponds to the trend of all other areas which do not belong to this cluster in question. It is valid to highlight that the TTI and TTE found in this area were statistically significant in this analysis and not the cluster itself. Therefore, the 95%CI were not calculated for this analysis[18].

**Ethical aspects**

The study was approved by the Research Ethics Committee of the Ribeirão Preto College of Nursing from the University of Sao Paulo, under the Presentation Certificate for Ethical Appreciation nº 3,836,401 obtaining a Presentation Certificate of Ethical Appreciation number: 24963319.1.0000.5393, issued on. February 13, 2020.

## 3. Results

From 2008 to 2018, 29,499 TB cases were reported in the state of Paraná, of which 32.41% (n=9.561) used some type of psychoactive substance, with alcoholism being 45.78% (n=6.014), smoking 32.09% (n=4,216) and other drug use 22.13% (n=2.903).

When analyzing the sociodemographic characteristics of TB cases among users, we observed a higher prevalence of male sex, age from 30 to 59 years, race/white color, up to 8 years of study (Table 1).

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**Table 1.** Clinical characteristics of TB patients, Paraná, Brazil (2008-2018).

| Variables | Absolute frequency (n=9561) | Relative frequency (%) | Rate (100.000 inhabitants) |
|---|---|---|---|
| **Sex** | | | |
| Male | 7723 | 80.78 | 80776.07 |
| Female | 1838 | 19.22 | 19223.93 |
| **Age group** | | | |
| < 15 years | 83 | 0.87 | 868.11 |
| 15 to 29 years | 1994 | 20.86 | 20855.56 |
| 30 to 59 years | 6517 | 68.16 | 68162.33 |
| > 60 years | 967 | 10.11 | 10114.00 |
| **Race** | | | |
| White | 5750 | 60.14 | 60140.15 |
| Black | 848 | 8.87 | 8869.37 |
| Yellow | 84 | 0.88 | 878.57 |
| Brown | 2643 | 27.64 | 27643.55 |
| Indigenous | 52 | 0.54 | 543.88 |
| **Schooling** | | | |
| Illiterate | 375 | 3.92 | 3922.18 |
| Up to 8 years of study | 6.461 | 67.60 | 18899.70 |
| More than 8 years of study | 2.345 | 24.50 | 10720.64 |
| **Case type** | | | |
| New case | 7658 | 80.1 | 80096.22 |
| Recurrence | 689 | 7.21 | 7206.36 |
| Reinstatement after abandonment | 612 | 6.4 | 6401 |
| Transfer | 555 | 5.8 | 5804.83 |
| **Classification** | | | |
| Pulmonary | 8307 | 86.88 | 86884.22 |
| Extrapulmonary | 977 | 10.22 | 10218.6 |
| Pulmonary + extrapulmonary | 277 | 2.9 | 2897.19 |
| **Sensitivity test** | | | |
| Resistant to isoniazid only | 112 | 1.17 | 1171.43 |
| Resistant to rifampicin | 16 | 0.17 | 167.35 |
| Resistant to isoniazid and rifampicin | 29 | 0.3 | 303.32 |
| Resistant to other 1st-line drugs | 35 | 0.37 | 366.07 |
| Sensible | 1053 | 11.01 | 11013.49 |
| **Closing status** | | | |
| Cure | 6408 | 67.02 | 67022.28 |
| Abandonment | 1116 | 11.67 | 11672.42 |
| Death from TB | 451 | 4.72 | 4717.08 |
| Death from other causes | 621 | 6.5 | 6495.14 |

 doi:10.20944/preprints202204.0010.v1

| | | | |
|---|---|---|---|
| DR-TB | 212 | 2.22 | 2217.34 |

Regarding the clinical characteristics of TB cases described in Table 1, the majority corresponded to new and pulmonary cases and were sensitive to the available medication. As for the outcome, most cases evolved to cure, and it was still observed that 11.67% had abandoned treatment.

In Figure 2, we observed 6.014 cases of TB and alcoholism with an incidence rate of 5.4 cases/100.000 inhabitants. According to the analysis result, an annual growth of 0.58% was identified in Paraná. From the EVPP analysis, it is possible to observe the conformation of 8 clusters of spatial risk, elucidated in Figure 2A, in the West, Northwest, Pioneer North, and Metropolitan of Curitiba.

Figure 2B shows the Hotspots obtained from the SVTT analysis for TB, in which it is possible to observe a protective cluster in the Northwest *Paranaense* mesoregion with TTI above 999% and TTE = 0.57% growth per year. Still, on the SVTT, two risk clusters were observed, with cluster 2 in the Central North mesoregion, with TTI = 50.51 annual growth and TTE = 0.30% growth per year and cluster 3 in the Metropolitan region of Curitiba, with TTI = 6.6% and TTE = 0,20%, both showed annual growth.

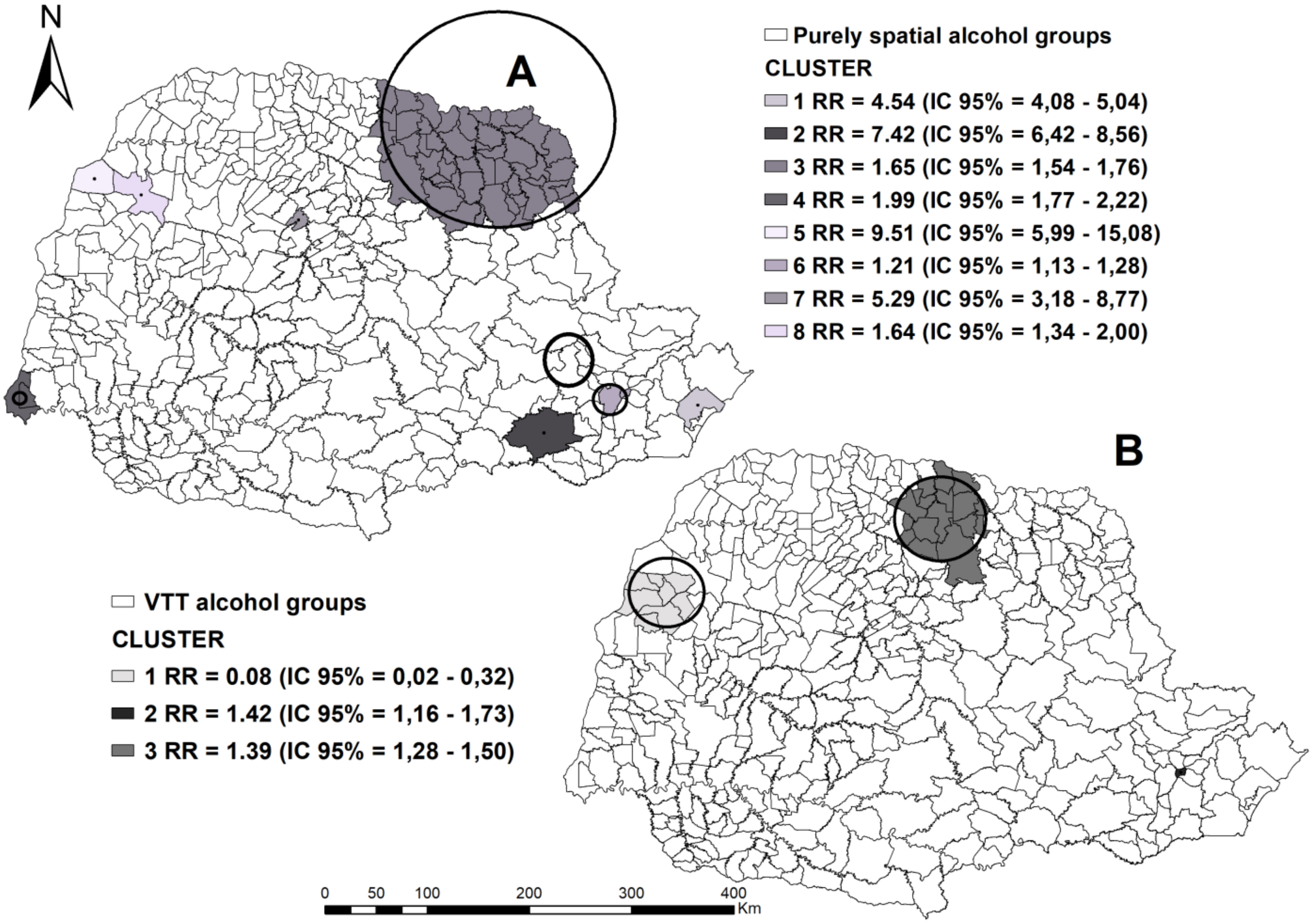


**Figure 2.** Areas of spatial risk for tuberculosis in alcohol users, by municipalities, state of Paraná (2008-2018).

There were 4.216 cases of TB and smoking, whose incidence rate was 3.8 cases/100.000 inhabitants, and there was an annual growth of 37.08% in the state in the

Sof Stats (Figure 3). The EVPP identified 7 clusters of spatial risk in the West, Northwest, Central, and Metropolitan North regions of Curitiba (Figure 3A).

The SVTT for this condition pointed to two risk Hotspots, with cluster 1 extending from the West to the Northwest mesoregion, with TTI = 70.8 annual growth and TTE = 35.7% growth per year, and cluster 2 in the Metropolitan region of Curitiba with LLR= 21,6, TTI = 52.7% and TTE = 34.8% annual growth (Figure 3B).

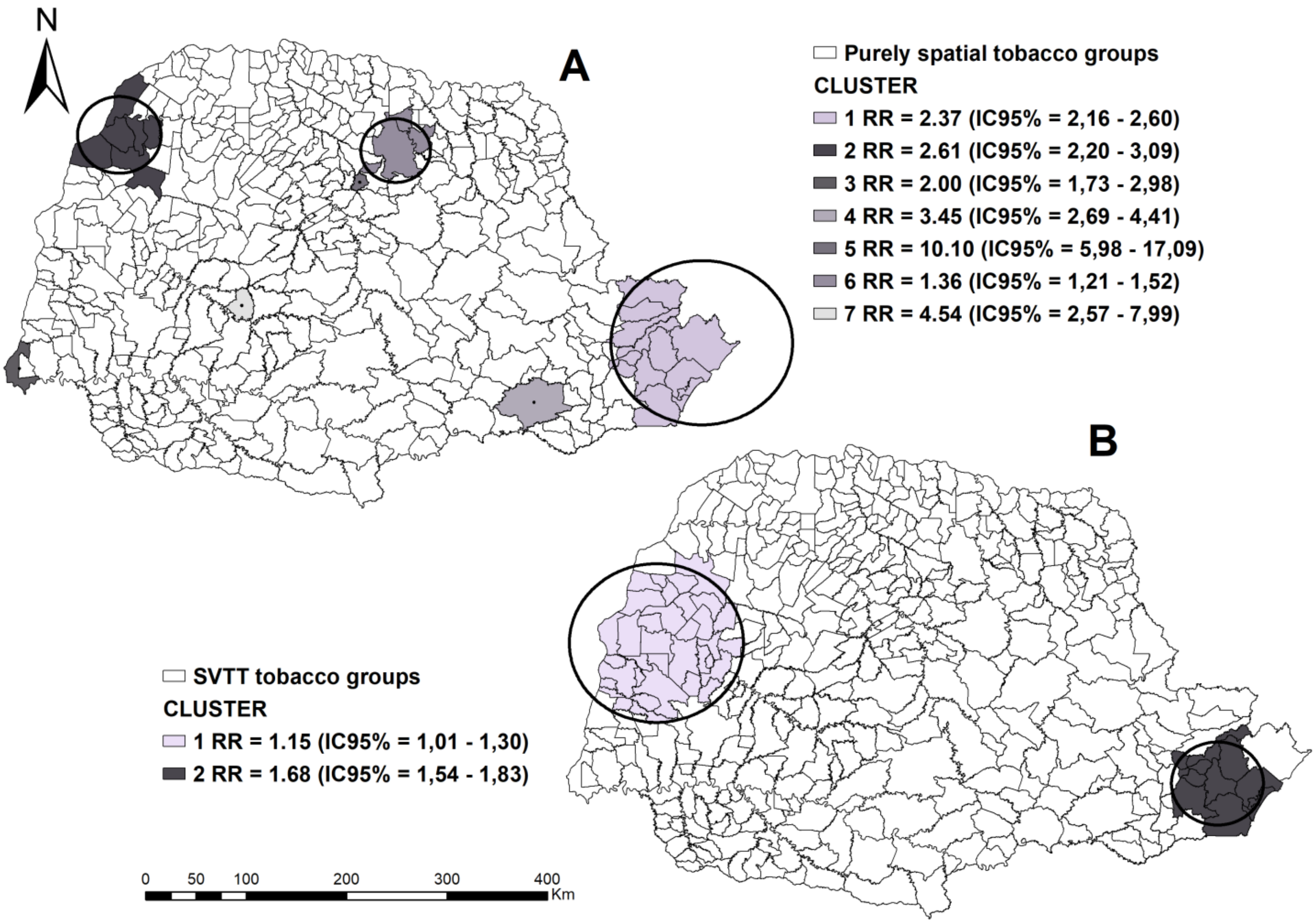


**Figure 3**. Areas at spatial risk for tuberculosis in tobacco users, by municipalities, state of Paraná (2008-2018).

Regarding TB cases and the use of other drugs, we obtained 2.903 cases, and the incidence rate was 2.6 cases/100.000 inhabitants, and 19.41% annual growth in the state (Figure 4). Figure 4A represents the EVPP, which identified 5 clusters of spatial risk in the West, Central North, and Metropolitan regions of Curitiba.

As shown in Figure 4B, the SVTT analysis for TB and other drugs identified two protection clusters and one at-risk cluster. The protection cluster 1 reached the entire length of the Western, Northwest, Western Center, South, and Southwest mesoregion, with TTI = 36.7% of annual growth and TTE = 16.3% of growth per year, and cluster 3 in the Metropolitan mesoregion of Curitiba, TTI of 37.3% and TTE of 18,5 % annual growth. Cluster 2 of risk is located on the boundary between the Norte Pioneer and Centro

Oriental mesoregions, with TTI of 70.8% of annual growth and TTE of 35.7% of growth per year.

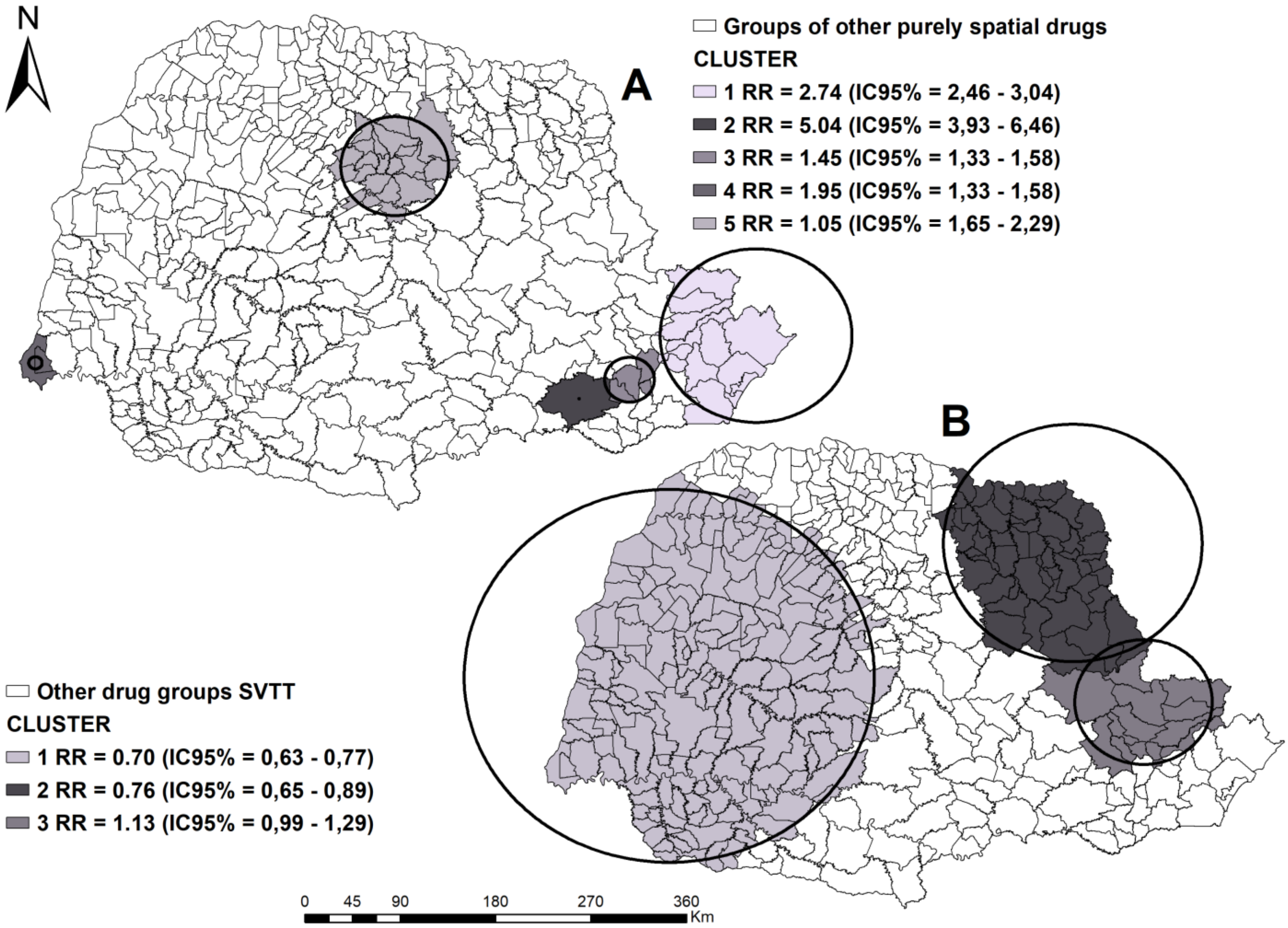


**Figure 4.** Areas of spatial risk for tuberculosis in users of other drugs, by municipalities, state of Paraná (2008-2018).

## 4. Discussion

The study aimed to identify Hotspots of peoples diagnosed with tuberculosis and abusive use of alcohol, tobacco and other drugs on communities through a geospatial intelligence application. According to the results, it was identified Hotspots in accordance with type of drug used by people with TB; this may be associated to the social determinants of the different regions and/or territories identified.

There were spatial variations in the temporal trends of alcohol, tobacco, and other drugs, showing that the phenomenon is growing in this territory. The incidence of TB cases associated with alcohol, tobacco, and other drugs was also verified, with a heterogeneous distribution between the state's different regions.

TB is historically known for its direct relationship with social determinants in health and for reaching the most vulnerable population groups, a factor that requires an individualized, collective, and programmatic health strategy for its elimination[17].

Among the different risk factors that hinder/favor the development of TB, alcohol stands out. Alcohol consumption is an ancient practice and is part of the socio-historical process of humanity. However, this habit, in excess, can generate negative consequences such as chemical dependence, development of more than 60 types of acute and chronic diseases, including TB[19].

The use of alcohol/alcoholism is a determinant with a strong association for the development of TB, a condition identified in this study, being 45.78% of the population with TB alcoholics. Studies developed in Singapore[20], Germany[21], Ethiopia[22], India[23], and Brazil[6,10,24] presented the same specificities, alcoholism being a risk factor for TB as well as worse treatment outcomes.

Alcohol consumption is a negative factor for the prognosis of TB since it triggers difficulty in treatment adherence, interruptions in the use of medicines, and deaths[9]. When an individual does not adhere to the treatment of TB, this contributes significantly to the increase in the number of new cases in geographical space[24]. Therefore, the consumption of alcohol and other drugs can aggravate the non-adherence to treatment, the transmission of the disease, and cause death.

In a randomized clinical trial developed in India[23], which sought to demonstrate the feasibility of using intervention regarding alcohol consumption among patients with TB, it was evidenced that in the intervention group, the results were significantly better ($p = 0.02$) when treatment adherence was identified.

This study showed a relationship between TB and smoking since 14.29% reported cases were smokers. It is estimated that about 1.3 billion people worldwide make active use of tobacco, with a higher incidence in underdeveloped or/in developed countries. Consequently, these countries have a high TB rate[25].

Tobacco is also understood as an important risk factor for TB, and the exposure to cigarette smoke increases three times the chances of developing TB[26]. Among smokers, the risk of latent TB increases 1.6 times. In active TB, the risk is two times higher for the development of the disease, while the chance of death is 2.6 times higher. It is also worth mentioning that the chances for development and worsening/death increase significantly with the time of consumption in years, the number of cigarettes used per day, and the socioeconomic level[27; 28].

Among the cases of TB in the state, 22.13% were users of other drugs/illicit. Knowing the direct relationship between TB and social determinants of health, it is known that the population using illicit and injectable drugs have a greater vulnerability to TB infection and a worse outcome in treatment, and often these users find an environment of marginalization on the streets and lacking access to health services[24].

The use of illicit drugs causes numerous problems in the health of the population, as well as decreases the immune response of the body, and consequently increases the likelihood for the development of TB, and among those diagnosed with the disease have a higher bacillary burden and likelihood of developing drug resistance[29], related to lack of demand/access to health services and difficulty in performing the recommended TB treatment. Expansion of the teams of offices in the street, as well DOTS for these people may contribute to reduce the adverse health, social, and economic consequences of illicit drug use, without necessarily reducing consumption [28,29].

Spatial clusters are multicausal, and it is important to understand that they are neither stagnant nor homogeneous, within the spatial cluster itself, there is a difference of relative risk, both decrease and growth, therefore it is important to realize more than one methodology to be able to characterize the agglomeration.

The originality of this study is allowing health managers and workers to direct specific actions to the population who is addicted to alcohol and other drugs, as well as knowing the epidemiological scenario and developing strategies to promote a reduction in the TB transmission cycle and development of new cases [30] as well treatment abandonment, death, and multidrug-resistant TB[24].

The main limitation of this study include the use of secondary data, which are not free of incomplete data. However, Sinan is considered a reliable source for developing studies of this nature.

## 5. Conclusions

The study advanced in knowledge by evidencing the most vulnerable territories to the problem and, as the TB comorbidity and use of alcohol and other drugs have been conformed over time in these territories; with this evidence can-if, it gives rise to reflections on the measures implemented in these regions and how much they have had an effect.

The study brings evidence available today to the panels defined by the Ministry of Science and Technology for the adoption and definition of public policies. It is also expected that the results are reversed in updating projects of the teams that today are on the front line of TB and that they recognize themselves in the process and can think of more comprehensive work projects, and that includes mental health, as a possibility of joint work and intersectoral actions. The elimination of TB is based on the United Nations (UN) Sustainable Development Goals and the End TB Strategy. Thus, the solution pervades integrated actions and glimpses its interprofessional and intersectoral care.

## 6. Patents

Not applicable

**Author Contributions:** Conceptualization, ARS, JDA and RAA.; methodology, ARS, JDA, TZB and RAA.; software, ARS and ACVR.; formal analysis, ARS, JDA, TZB, ACVR and RAA.; investigation, ARS.; data curation, ARS, JDA, TZB, ACVR and RAA.; writing—original draft preparation, ARS.; writing—review and editing, ARS, FMD, MFT and RAA.; supervision, RAA.; project administration, ARS.; All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** The study was approved by the Research Ethics Committee at the University of São Paulo at Ribeirão Preto College of Nursing under Certificate of Presentation for Ethical Consideration number 24963319.1.0000.5393 and report number 3.836.401, issued on February 13th 2020 in accordance with the Guidelines and Regulatory Standards for Research with Human Subjects, Resolution number 466/2012 of the National Health Council of Brazilian Ministry of Health.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author on reasonable request.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References


1. Thomas BE, Thiruvengadam KSR, Kadam D, Kadam D, Ovung S, Sivakumar S, et al. CTRIUMPH-RePORT India Study. Smoking, alcohol use disorder and tuberculosis treatment outcomes: A dual co-morbidity burden that cannot be ignored. PLoS One. **2019**, 14, e0224914. doi: 10.1371/journal.pone.0220507.
2. World Health Organization (WHO). Global tuberculosis report. New York: WHO; 2020. Disponível em: <Disponível em: https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment >. Acesso em: 11 de julho de 2021. »https://www.who.int/publications/i/item/9789240001503.
3. Ministry of Health. Health Surveillance Department. Epidemiological Bulletin. Tuberculosis. Brazil; 2021. Brasília: Health Surveillance Secretariat; 2021. Available from: https://www.gov.br/saude/pt-br/media/pdf/2021/marco/24/boletim-tuberculose-2021_24.03.
4. Cecilio HPM, Santos AL, Marcon SS, Latorre MRDO, Mathias TAF, Rossi RM. Tuberculosis mortality trend in the state of Paraná, Brazil – 1998-2012. Cien Saude Colet. **2018**, 23, 241-48. doi: 10.1590/1413-81232018231.25242015.
5. Reis-Santos B, Shete P, Bertolde A, Sales CM, Sanchez MN, Arakaki-Sanchez D. et al. Tuberculosis in Brazil and cash transfer programs: A longitudinal database study of the effect of cash transfer on cure rates. PLoS One. **2019**, 14, e0212617. doi: 10.1371/journal.pone.0212617.
6. Alves JD, Arroyo LH, Arcoverde MAM, Cartagena-Ramos D, Berra TZ, Alves LS, et al. Magnitud de los determinantes sociales en el riesgo de mortalidad por tuberculosis en el Centro-Oeste de Brasil. Gac Sanit. **2020**, 34, 171-78. doi: 10.1016/j.gaceta.2019.01.004.
7. Shimeles E, Enquselassie F, Aseffa A, Tilahun M, Mekonen A, Wondimagegn G, Hailu T. Risk factors for tuberculosis: A case-control study in Addis Ababa, Ethiopia. PLoS One. **2019**, 14, e0214235. doi: 10.1371/journal.pone.0214235.
8. Nguipdop-Djomo P, Rodrigues LC, Smith PG, Abubakar I, Mangtani P. Drug misuse, tobacco smoking, alcohol and other social determinants of tuberculosis in UK-born adults in England: a community-based case-control study. Sci Rep. **2020**, 10, 5639. doi: 10.1038/s41598-020-62667-8.
9. Myers B, Bouton TC, Ragan EJ, White LF, McIlleron H, Theron D, et al. Impact of alcohol consumption on tuberculosis treatment outcomes: a prospective longitudinal cohort study protocol. BMC Infect Dis. **2018**, 18, 488. doi: org/10.1186/s12879-018-3396-y.
10. Arroyo LH, Yamamura M, Ramos ACV, Campoy LT, Crispim JA, Berra TZ, et al. Determinants of multidrug-resistant tuberculosis in São Paulo-Brazil: a multilevel Bayesian analysis of factors associated with individual, community and access to health services. Trop Med Int Health. **2020**, 25, 839–49. doi: 10.1111/tmi.13409.
11. Ministry of Health. Secretariat of Science, Technology, Innovation and Strategic Inputs in Health. Department of Science and Technology. Methodological guideline: synthesis of evidence for policies. Brasilia: Brazil, 2020.
12. Kulldorff M, Nagarwalla N. Spatial disease clusters: Detection and inference. Stat Med. **1995**, 14, 799-810. doi:10.1002/sim.4780140809.
13. Chen J, Qiu Y, Yang R, Li L, Hou J, Lu K, et al. The characteristics of spatial-temporal distribution and cluster of tuberculosis in Yunnan Province, China, 2005–2018. BMC Public Health. **2019**, 19, 1715. doi: 10.1186/s12889-019-7993-5.
14. Lucena SEF, Moraes RM. Detection of space-time cluster of homicides by stabbing in the João Pessoa city, Paraíba state, Brazil. Bol. Ciênc. Geod. **2012**, 18, 605-23. doi: 10.1590/S1982-21702012000400006.

15. Prates MO, Kulldorff M, Assunção RM. Relative risk estimates from spatial and space-time scan statistics: are they biased? Stat Med. **2014**, 33, 2634-44. doi: org/10.1002/sim.6143.
16. Moraga P, Kulldorff M. Detection of spatial variations in temporal trends with a quadratic function. Stat Methods Med Res. **2016**, 25, 1422–37. doi: 10.1177/0962280213485312.
17. André SR, Nogueira LMV, Rodrigues ILA, Cunha TN, Palha PF, Santos, CB. Tuberculosis associated with the living conditions in an endemic municipality in the North of Brazil. Rev. Latino-Am. Enfermagem. **2020**, 28, e3343. doi: 10.1590/1518-8345.3223.3343.
18. Wagner MB, Callegari-Jacques SM. Association measures in epidemiological studies: relative risk and odds ratio. J. pediatr. **1998**, 247-51. Available from: http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&src=google&base=LILACS&lang=p&nextAction=lnk&exprSearch=220088&indexSearch=ID.
19. Reis AM, Quintal C, Lourenço Ó. Do drinking problems in the past affect current consumption?. Cad. Saúde Pública. **2019**, 35, e00025618. doi: 10.1590/0102-311x00025618.
20. Yap P, Tan KHX, Lim WY, Barkham T, Tan LWL, Chen MI, et al. Prevalence of and risk factors associated with latent tuberculosis in Singapore: A cross-sectional survey. Int J Infect Dis. **2018**, 72, 55-62. doi: 10.1016/j.ijid.2018.05.004.
21. Herzmann C, Sotgiu G, Bellinger O, Diel R, Gerdes S, Goetsch U, et al. TB or not TB consortium. Risk for latent and active tuberculosis in Germany. Infection. **2017**, 45, 283-290. doi: 10.1007/s15010-016-0963-2.
22. Desissa F, Workineh T, Beyene T. Risk factors for the occurrence of multidrug-resistant tuberculosis among patients undergoing multidrug-resistant tuberculosis treatment in East Shoa, Ethiopia. BMC Public Health. **2018**, 18, 422. doi: org/10.1186/s12889-018-5371-3.
23. Navya N, Jeyashree K, Madhukeshwar AK, Anand T, Nirgude AS, Nayarmoole BM, et al. Are they there yet? Linkage of patients with tuberculosis to services for tobacco cessation and alcohol abuse - a mixed methods study from Karnataka, India. BMC Health Serv Res. **2019**, 19, 90. doi: 10.1186/s12913-019-3913-8.
24. Espírito Santo SSS, Abreu AMM, Portela LF, Mattos LR, Paixao LAR, Brites RMR, et al. Psychoactive substance use in patients with tuberculosis: treatment adherence and interface with Brief Interventions. Rev. Enf. Ref. **2020**, serV, e19093-e19093. doi: org/10.12707/RIV19093.
25. Silva DR, Muñoz-Torrico M, Duarte R, Galvão T, Bonini EH, Arbex FF, et al. Risk factors for tuberculosis: diabetes, smoking, alcohol use, and the use of other drugs. J. bras. Pneumol. **2018**, 44, 145-152. doi: 10.1590/s1806-37562017000000443.
26. López-Hernández Y, Rivas-Santiago CE, López JA, Mendoza-Almanza G, Hernandez-Pando R. Tuberculosis and cigarette smoke exposure: An update of in vitro and in vivo studies. Exp Lung Res. **2018**, 44, 113-126. doi: 10.1080/01902148.2018.1444824.
27. Tewatia P, Kaushik RM, Kaushik R, Kumar S. Tobacco smoking as a risk factor for tuberculous pleural effusion: a case-control study. Glob Health Epidemiol Genom. **2020**, 5. doi: 10.1017/gheg.2020.1.
28. Aguilar JP, Arriaga MB, Rodas MN, Martins Netto E. Smoking and pulmonary tuberculosis treatment failure: a case-control study. J Bras Pneumol. **2019**, 45, e20180359. doi: 10.1590/1806-3713/e20180359.
29. Soboka M, Tolessa O, Tesfaye M, Adorjan K, Krahl W, Tesfaye E, et al. Magnitude and predictors of khat use among patients with tuberculosis in Southwest Ethiopia: A longitudinal study. PLoS One. **2020**, 15, e0236154. doi: 10.1371/journal.pone.0236154.
30. Rao VG, Bhat J, Yadav R, Muniyandi M, Bhondeley MK, Wares DF. Smoking and alcohol consumption: Risk factors for pulmonary tuberculosis among the tribal community in central India. Indian J Tuberc. **2017**, 64, 40-43. doi: 10.1016/j.ijtb.2016.11.009.