Transferring and Adapting a Prognostic Model to Improve Care of Brazilian Traumatic Brain Injury Patients

by

Jiawen Wu

Duke Global Health Institute

Duke University

Date:________________________

Approved:

____

João Ricardo Vissoci, Advisor

____

Catherine Staton

____

Luciano de Andrade

Thesis submitted in partial fulfillment of

the requirements for the degree of

Master of Science in the Duke Global Health Institute

in the Graduate School of Duke University

2020

ABSTRACT

Transferring and Adapting a Prognostic Model to Improve Care of Brazilian Traumatic Brain Injury Patients

by

Jiawen Wu

Duke Global Health Institute

Duke University

Date:________________________

Approved:

____

João Ricardo Vissoci, Advisor

____

Catherine Staton

____

Luciano de Andrade

An abstract of a thesis submitted in partial

fulfillment of the requirements for the degree

of Master of Science in the Duke Global Health Institute

in the Graduate School of Duke University

2020

Abstract

Background: Traumatic brain injury (TBI) is a major cause of death and disability. About 10 million people annually are affected by TBI, with a prominent burden in low- and middle-income countries (LMICs). In Brazil, TBI is responsible for 125,500 admissions and 9700 hospital deaths annually. The poor prognosis could be caused by insufficient neurosurgeons and diagnostic machines. This study aims to find an optimum TBI prognostic model to serve as a diagnostic tool that can be adapted from prior work in Tanzania to Brazil. We aim to develop an effective TBI prognostic model that could be generalized in LMICs.

Methods: The study was a secondary data analysis on clinical and sociodemographic variables of 3209 TBI patients at Kilimanjaro Christian Medical Center (KCMC) and 752 TBI patients at Hospital Santa Casa de Maringá. We trained and tested eight machine learning models using three strategies: 1) using Tanzanian dataset trained models to test Brazilian dataset, 2) using Tanzanian-Brazilian combined dataset for training and testing and 3) using Brazilian dataset for training and testing. We compared the performance of models using confusion matrix statistics: area under the ROC curve(AUC), sensitivity, specificity, positive predictive value, negative predictive value and accuracy.

Findings: Models using Tanzanian-Brazilian combined dataset for training and testing outperformed models of other two strategies. The AUC of the models varied from 80.9% (K nearest neighbor) to 91.9% (Random Forest). The optimum model, Random Forest, had a strong predictive power of classification with sensitivity of

0.92, specificity of 0.77, positive predictive value of 0.96, negative predictive value of 0.61 and accuracy of 0.90.

Interpretations: Our study shows the successful adaptation of the TBI prognostic model from Tanzania to Brazil. Additionally, it indicates the possibility of generalizing a TBI prognostic model to LMICs. With larger multi-national data, we hope to develop an effective model that could accurately predict the potential outcome of TBI patients. The model could serve as a powerful auxiliary tool for diagnosis and help reduce mortality of TBI patients in LMICs.

Source of Funding: The project is conducted with the funding from Duke Global Health Institute.

Contents

List of Tables

List of Figures

Acknowledgements

I would like to acknowledge the professional guidance and warm support from my committee members: Dr. Vissoci, Dr. Staton and Dr. Andrade. Additionally, I would like to acknowledge Amanda, Cyrus, Yolande, Pedro, Lincoln, Luis, Gi as well as other Brazilian students who taught me the amazing machine learning techniques and geographic information system mapping. I really appreciate the feedback from Dr. Egger and Dr. Herring for my thesis as well as the support from DGHI education team. Last but not least, many thanks for the love from my family and friends, which keeps me tough and confident.

1. Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability globally. About 10 million people are affected annually by TBI, with a prominent burden in low- and middle-income countries (LMICs). (Hyder, 2007) TBI leads to substantial social and economic costs, which exerts burden on victims, their families as well as the whole society.

Understanding the unique interplay between socioeconomic status, healthcare accessibility and demographics is essential to promote evidence-based policy for reducing TBI related morbidity and mortality. Studies have shown that most TBI patients are males, urban dwelling, of lower income levels, and involved in falls or motor vehicle crashes. In high-income countries (HICs), TBI primarily happens among automobile drivers while in low- and middle-income countries (LMICs), TBI patients are more likely to be pedestrians, cyclists, and motorcyclists. (Rutland-Brown et. al, 2006; Liao et. al, 2012; Shao, 2012; Harrison et. al, 2013; Jourdan et. al, 2013; Roozenbeek, Maas, & Menon, 2013; Walder et. al, 2013; Khan et. al, 2015). Other studies indicate that TBI is also associated with alcohol and substance assumption. Regarding the severe burden of TBI, it is paramount to analyze the real-world data to promote effective intervention on reduction of TBI mortality.(Roozenbeek, Maas, & Menon, 2013)

1.1 Current state of the literature

1.1.1 Brazil and its burden of TBI

Brazil, a middle income country, is the largest and most populated country in South America, with 206 million inhabitants and 21% of the population living below the poverty line (CENSUS 2010). The country is composed of five regions: north, northeast, south, southeast, and central-west regions. They differ significantly in population density, demographics, socioeconomic status, and healthcare infrastructure. Brazil has one of the highest Gini (Ceriani, L, 2012) indices in the world, indicating a large gap between the rich and the poor. For example, the southeast region accounts for only 11% of the Brazilian territory but 56% of the country's GDP and 43% of the population. (Paim, 2011, Azzoni, 2001) The southeast region has the most dense population, more urban centers, lower proportions of the population living below the poverty line, higher education level, as well as more accessibility to healthcare infrastructure. On the other hand, the majority of the north region is covered with Amazon forests, with less population, a higher proportion of people living below the poverty line, less education level, and limited accessibility to healthcare infrastructure. Despite the presence of a universal healthcare system in Brazil, there are significant regional and local disparities in resources, funding, and access to care (Garcia-Subirats, 2014; da Silva, 2011; Viacava, 2016).

TBI stands out as a grave public health problem in Brazil, responsible for 125,500 admissions and 9700 hospital deaths annually (Almeida et. al,2015). The majority of TBI patients in Brazil are either between 20 to 29 years of age or over age 70, being male, living in urban areas, not using protective equipment like helmet, and being of white race (Mello, 2005; Rocha, 2006; Faria; 2008; Ramos, 2010; Moura, 2011). A study in the southern city of Florianópolis in Brazil analyzed data from severe TBI patients admitted between 1994 to 1995 and 2000 to 2001, and showed a decrease in the proportion of automobile crash victims from 33% to 12.8% while an increase in motorcycle crash victims from 13% to 30.7%. (Martins, Silva & Coutinho,

2003) The authors suggested transition of TBI mortality was due to seat belts use, the introduction of the 1998 national traffic codes, and better health care.

1.1.2 TBI prognostic model

One way to reduce the burden of TBI mortality is immediately appropriate medical intervention based on accurate diagnosis. Previous studies have developed various predictive models for TBI survival and outcome to support clinical decision. The Trauma and Injury Severity Score (TRISS) model was developed to predict survival for TBI patients in 1987 (Maeda et. al,2019). Similarly, study conducted in Edinburg from 1989 to 1991, used multivariate logistic regression model to predict the 1-year survival based on predictors of age, GCS, injury severity, pupil reactivity and presence of haematoma on CT among moderate and severe TBI patients (Signorini et. al, 1999). Recently, the Corticosteroid Randomization After Significant Head Injury (CRASH) and the International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) are developed to predict TBI outcome (Maeda et. al,2019). In another study in Taiwan, neural network models were evaluated to be better than logistic models in predicting the possibility of open-skull surgery based on predictors as GCS, types of skull fracture and episode of convulsion among TBI patients (Li et. al, 2000).

Study in Japan shows TRISS, IMPACT and CRASH correctly predicted in-hospital mortality and six month outcome for TBI patients, which indicated their strong external validity (Maeda et. al, 2019). However, most predictive models are adapted to the high-income countries setting and there is limited literature on the development and validation of TBI predictive models in low- and middle-income countries (LMICs). A systematic review on TBI prognostic models identified 102 models, among which only 5 models for LMICs (Perel et. al, 2006). Given the prominent TBI burden and limited healthcare resources in LMICs, it is necessary to develop and adapt TBI prognostic models in LMICs to help risk triage.

1.2 Purpose of this project

The project is composed of two individual but complementary studies. One study is to measure how socioeconomic status, demographics, and accessibility to healthcare infrastructure are associated with five-year TBI mortality rate through a cross-sectional study of Brazilian national health system data. We hypothesize that high TBI mortality is significantly related with motorcycle fleet registry and accessibility to healthcare infrastructure. To our knowledge, this is the first study to evaluate TBI mortality rate at national level. Given the unequal distribution of healthcare resources in Brazil and other LMICs, we came up with an idea to develop a generalized TBI prognostic model to support risk stratification and decision making. Therefore, it can help offer timely medical treatment to TBI patients according to their severity of injury and improve their prognosis.

Thus, the second study is to find an optimum TBI prognostic model to serve as a auxiliary diagnostic tool that can be adapted from prior work in Tanzania to Brazil. We want to externally validate the model using both Tanzanian and Brazilian datasets. The objective is to develop an effective TBI prognostic model that could be generalized in LMICs.

2. Methods: framework of the project

We have methods for these two projects respectively. The project is composed of two studies. One study is to conduct a 5-year spatio-temporal epidemiologic analysis about traumatic brain injury including socioeconomic characteristics in Brazil, which is referred to as five-year TBI mortality in the following. The other study is to transfer and adapt a prognostic model to improve care of Brazilian traumatic brain injury patients, which is referred to as TBI prognostic model in the following.

2.1 Setting

2.1.1 five-year TBI mortality

Brazil, a middle income country, is the largest and most populated country in South America, with 206 million inhabitants and 21% of the population living below the poverty line. [18] (CENSUS 2010). The country is composed of five regions: north, northeast, south, southeast, and central-west regions. They differ significantly in population density, demographics, socioeconomic status, and healthcare infrastructure.

2.1.2 TBI prognostic model

The Tanzania-only algorithm was developed based on the clinical data collected from 3961 patients admitted for TBI at KCMC hospital in Moshi, Tanzania from 2013 to 2017. This dataset and algorithm were already established before this study. The Tanzania-only model is based on Bayesian Generalized Linear Model which has the AUC of 86.5%. The model has a “moderate to high capability of predicting a good recovery and an intermediate ability of predicting a bad recovery.” KCMC is a tertiary-level hospital serving a population of over 15 million people in north-western Tanzania and a primary point for treating TBI patients .

The Tanzanian+Brazilian combined and the Brazilian-only algorithm will be incremented based on clinical data collected from Hospital Santa Casa de Maringá. The hospital, established in the 1950s, now had 266 beds, a reference for the population of Maringa and surrounding regions.

2.2 Participants

2.2.1 five-year TBI mortality

We include patients who died from all categories of TBI (ICD-10 code “S00” to “S09” and its subgroups) who aged from 15 to 59 from 2013 to 2017. This age was chosen to incorporate working age adults who are also the most likely to suffer non-fall related traumatic brain injuries in this setting.

2.2.2 TBI prognostic model

We included patients who present for acute management of TBI to hospitals’ Emergency Department (ED) within 24 hours of injury survived to evaluation in the ED from May 2014 to April 2017. Patients who had missing data in the following key variables: admission date, discharge date, received surgery for TBI, and admission Glasgow coma scale (GCS) were excluded from the study.

2.3 Procedures

2.3.1 five-year TBI mortality

There are overall six datasets, including TBI mortality data, population, socioeconomics, vehicle fleet registry, intensive care units(ICU) beds and neurosurgeons. TBI mortality data was filtered by patients who died from all categories of TBI(ICD-10 code “S00” to “S09” and its subgroups) who aged from 15 to 59. This data was extracted from Sistema de Informação Hospitalar Descentralizada(SIHD), made available by DATASUS (SIHD, 2015). Population data was obtained from The Brazilian Institute of Geography and Statistics and sociodemographic data which contained income ratio, aging rate, Gini index, density ratio, occupancy and displacement rate and education was available from the United Nations Development Program. For the vehicle fleet registry, we got access to the data from the National Vehicles Department. Finally, we collected the data on available ICU beds and neurosurgeons over the country from the National Register of Health Facilities.

2.3.2 TBI prognostic model

Field workers have been collecting neurosurgical data for TBI in-hospital patients at Brazilian hospital since June 2016. The Brazilian dataset we used in this study is a de-identified registry composed of 752 TBI patients from Hospital Santa Casa de Maringá. Tanzanian dataset is a de-identified registry composed of 3209 TBI patients at KCMC in Moshi, Tanzania from 2014 to 2017. Both datasets covered over 100 clinical and social data for each patient, which were collected from a survey which included information on demographics, vital signs, mechanism of injury, type of treatment received, and patient outcome.

2.4 Study variables

2.4.1 five-year TBI mortality

In order to explore the risk factors for TBI mortality in Brazil from 2013 to 2017, we studied socio demographic variables, which included registry of two-wheel vehicles, registry of four-wheel vehicles and registry of giant vehicles, income ratio (IR), aging rate (AR), GINI coefficient, density ratio (DR), occupancy and displacement rate (ODR) and education level (EL) and healthcare variables which includes accessibility to intensive care unit (ICU) beds and accessibility to neurosurgeons.

2.4.2 TBI prognostic model

The initial input predictors were age, gender, mechanism of injury, alcohol use, AVPU (alert, responds to verbal, responds to pain, unresponsive), vital signs (temperature, respiratory rate, pulse, systolic blood pressure, diastolic blood pressure, pulse oxygen), total Glasgow coma score, reaction of pupil, casualty department disposition, whether had TBI surgery for TBI, whether had other surgery, whether went from surgery ward to ICU.

The outcome variable was measured as Glasgow outcome scale extended (GOSe) score at patient discharge. The GOSe ranges from scores of 1 to 8, where 1 represents death while 8 represents upper good recovery. We defined poor outcomes as GOSe from 1 to 6 while good outcomes were 7 to 8.

2.5 Analysis

2.5.1 five-year TBI mortality

Spatial autocorrelation evaluates the pattern of data aggregated by cities using exploratory spatial data analysis techniques (ESDA) in GeoDa. We created a spatial weight matrix-the binary matrix-type Queen to measure the non-random spatial association for TBI mortality. Univariate analysis of TBI mortality for each city assessed by the Global Moran Index measures the spatial dependence patterns in a global aspect. The value of the Index varies from -1 to +1 which refers to regions with negative spatial autocorrelation to regions with positive spatial autocorrelation. In this study, regions with negative spatial autocorrelation refers to cities are surrounded with cities with different TBI mortality while positive spatial autocorrelation means cities are surrounded with cities with similar TBI mortality. However, a limitation of Global Moran Index is that it may mask the patterns of local spatial association, since a negative value of Global Moran Index does not mean a lack of positive spatial association among cities. Therefore, local indicators of spatial association (LISA) method was used to explore cluster dependence in a local aspact. To measure the impact of healthcare on TBI mortality, Two Step Floating Catchment Area (2SFCA) was used to create accessibility to ICU beds and neurosurgeons as the surrogate of accessibility to health care using provider to population ratio as an accessibility index.

All the variables including TBI mortality, sociodemographics and vehicle fleet registry were standardized by population for each city. To detect the potential risk factors for TBI mortality, Ordinary Least Squares(OLS) Estimation was used to explore the risk factors in a global aspect. Furthermore, GWR was conducted using softwares of GWR4 to analyze the risk factors for TBI mortality locally, taking the variation of location into consideration.

2.5.2 TBI prognostic model

Three training strategies were developed to train and test the models. One strategy was merging the Tanzanian and Brazilian datasets together and using the combined dataset for training and testing. Another strategy was using Tanzanian dataset for training and Brazilian dataset for testing. The third strategy was using Brazilian dataset alone for training and testing.

We used the statistical language R for the analysis. All the datasets need to go through a data cleaning process before training and testing. Variables with more than 80% missing were removed from the datasets. Multiple imputation by chained equations was used to impute variables with less than 20% missing. Then, outliers like age older than 75, respiratory rate greater than 75, and systolic blood pressure greater than 220 mmHg were removed from the datasets. A high correlation analysis was performed and variables with correlation larger than 0.9 would be removed. The next step was to create dummy variables for categorical variables, followed by which, we checked and removed variables with near zero variance, high correlation and linear combos. Ultimately, we used data from 731 patients and 22 variables after all preprocessing steps for training strategy using Brazilian dataset alone for training and testing, data from 3873 patients and 24 variables after all preprocessing steps for training strategy using Tanzanian-Brazilian dataset for training and testing and 3140 patients and 15 variables after all preprocessing steps for training strategy using Tanzanian dataset for training and Brazilian dataset for testing.

Cross validation with 10 fold and 5 repetitions was used to splitting datas into training and testing dataset.

We tested eight different models: k-Nearest Neighbor, Ridge Regression, Neural Network, Bagged Tree, Bayesian Generalized Linear Model, Gradient Boosting Machine, Single C5.0 Ruleset and Random Forest. All methods were validated using an internal approach. The

kappa statistic was the metric used to assess the prognostic models built. Confusion matrix statistics was used for comparing the performance between models: area under the ROC curve (AUC)7, sensitivity, specificity, positive predictive value, negative predictive value.

3. Results

3.1 five-year TBI mortality

3.1.1 TBI mortality from 2013 to 2017

Our study population was composed of 180139 TBI patients aged 15 to 59 years old from 5558 cities in Brazil from 2013 to 2017. The average TBI mortality ranges from 0 to 130 per 100000 people, with high TBI mortality in north central-west, northeast and partial southeast regions of Brazil. Furthermore, the spatial analysis results from Global Moran Index and LISA indicated that there was a positive spatial association among cities that cities were surrounded by cities with similar value of TBI mortality(high or low) in both global and local aspects (figure 1). Additionally, clusters of cities with high TBI mortality rate was found mainly in central-west, northeast and partial southeast regions. The distribution and trend of TBI mortality did not change much over five years, with a consistent pattern among central-west and north regions and a decrease in the area of hotspots among southern region. (figure 2).

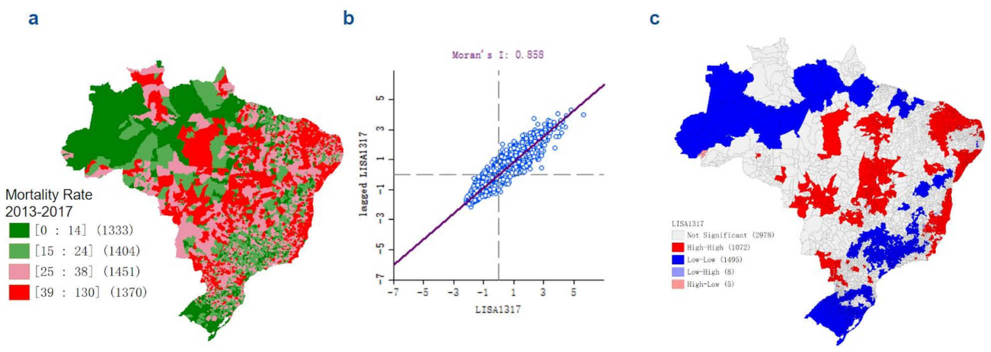


Figure 1. Spatial analysis of TBI mortality in Brazil. (a) Distribution of TBI mortality in Brazil over five years. (b) Global Moran Index for TBI mortality in Brazil over five years. (c) Local indicators of spatial association for TBI mortality in Brazil over five years.

.

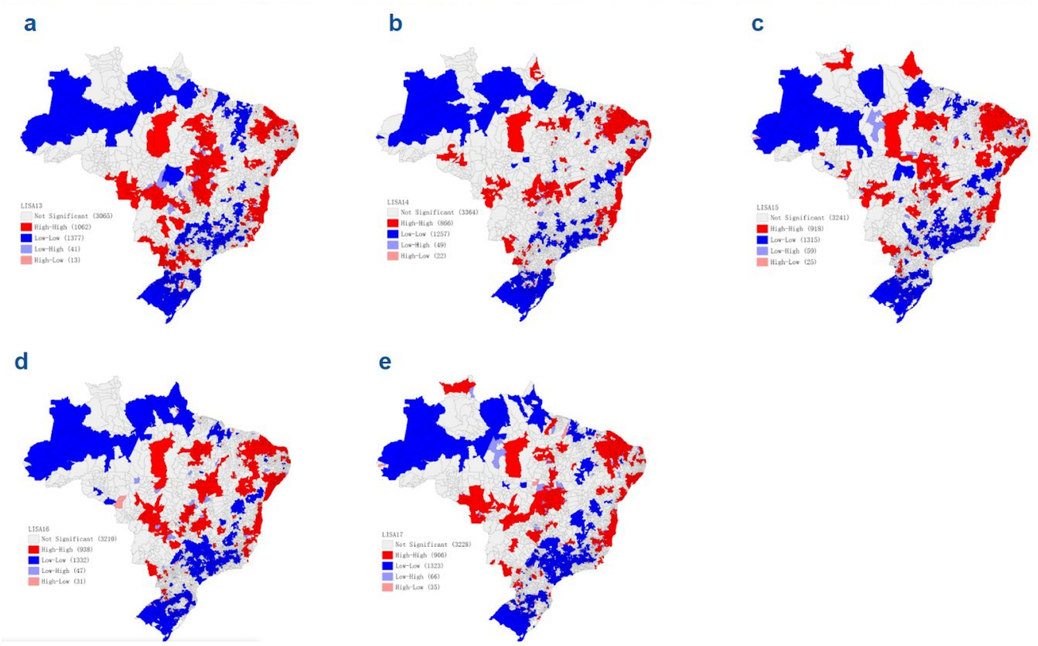


Figure 2. Local indicators of spatial association for TBI mortality in Brazil from 2013 to 2017. (a) Local indicators of spatial association for TBI mortality in 2013. (b) Local indicators of spatial association for TBI mortality in 2014 (c) Local indicators of spatial association for TBI mortality in 2015. (d) Local indicators of spatial association for TBI mortality in 2016. (e) Local indicators of spatial association for TBI mortality in 2017.

3.1.2 TBI mortality and vehicle fleet registry

The distribution of vehicle fleet registry over five years (figure 3). The vehicles were categorized into motorcycles, automobiles, and trucks. From the choropleth maps shown in figure 3, motorcycles were more prevalent in central-west, northeast, and partial southeast regions, which was consistent with the pattern of TBI mortality rate across the country. However, automobiles were more prevalent in the south region since southern regions are more developed and industrialized. Trucks are more used in southern and central-west regions. The central-west region was less industrialized and the land was mainly used for grazing and agriculture production. Therefore, trucks are the main transportation in the region.

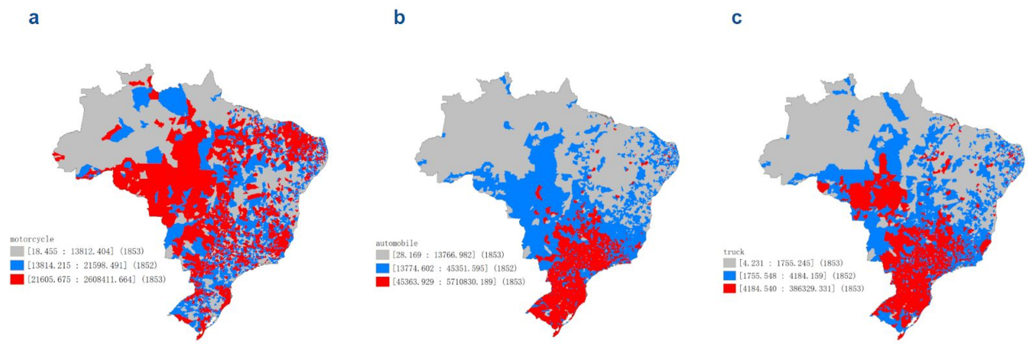


Figure 3. Comparison the distribution of different categories of vehicle fleet registry in Brazil over five years. (a) Distribution of motorcycle fleet registry in Brazil over five years. (b) Distribution of automobile fleet registry in Brazil over 5 years. (c) Distribution of giant vehicle fleet registry in Brazil over five years.

3.1.3 TBI mortality and health care

Accessibility to ICU beds, and neurosurgeons were calculated and visualized to assess the medical capacity (figure 4). As was shown in the graphs, there was higher accessibility to ICU beds in south and southeast regions, and higher accessibility to neurosurgeons in south, southeast, northeast while less and even no accessibility in other regions. Correspondingly, the TBI mortality was lower in south and southeast regions while relatively higher in other areas across the country.

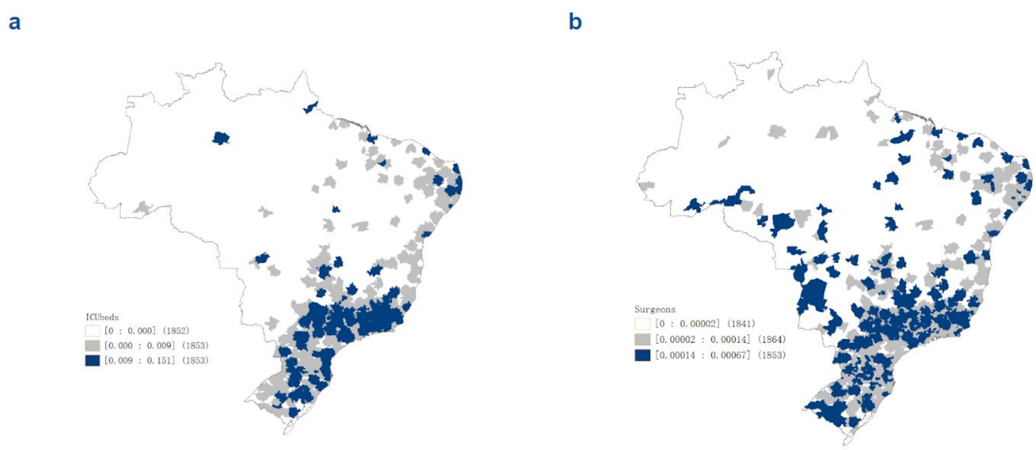


Figure 4. Visualization of the accessibility to ICU beds as well as neurosurgeons in Brazil over five years.(a) Accessibility to ICU beds in Brazil over five years. (b) Accessibility to neurosurgeons in Brazil over five years.

3.1.4 Geographically Weighted Regression(GWR)

Geographically Weighted Regression(GWR) was conducted to analyze the association between TBI mortality rate and sociodemographic factors, as well as health care capacity, varying by locality (figure 5). The GWR model explained about 42.21% of the variance in TBI mortality rate based on the value of adjusted R squared, which outperformed ordinary least squares regression models in our study. The distribution of beta coefficient and t-value were displayed to detect potential risk factors for high TBI mortality rate (figure 6, figure 7). According to both coefficient and t-value maps, for sociodemographic variables, motorcycles had a significantly positive coefficient of TBI mortality in mainly northeast,central-west and north regions which were less developed. However, among those same regions, an increase in the registry of automobiles was related to a decrease in TBI mortality rate. For trucks, there was a large area across central-west and north regions showing the registry of trucks was positively related with TBI mortality rate. Income ratio, GINI indices and occupancy and displacement rate all showed a significantly positive coefficient of TBI mortality rate in southeast and south regions, which indicates an inequality in economic development and wealth distribution. Aging rate had a significantly positive coefficient of TBI mortality rate in central-west region while density ratio had a significantly positive coefficient of TBI mortality rate in central-west, southeast and south regions. Education level had a significantly positive coefficient of TBI mortality in southeast and north regions. For healthcare variables, the accessibility to ICU beds and neurosurgeons had a significantly negative coefficient of TBI mortality in partial southeast, south, northeast and central-west regions. Limited accessibility to ICU beds had a significant positive coefficient of TBI mortality in northern regions and patients who were present at the health care center might be severely injured. However, accessibility to ICU beds and neurosurgeons also had significant positive coefficient of TBI mortality in partial northeast southeast and south regions. It was also related to inequality in economic development and resource distribution. Health care was aggregate in southern regions which were more developed. People living in poor cities had to come to the big cities in these regions to seek health care. This caused the demand to overwhelmingly exceed the supply and exerted a huge burden on medical capacity.

a

Global regression result
****

< Diagnostic information >

Residual sum of squares:	98165.283221
Number of parameters:	12
(Note: this num does not include an error variance term for a Gaussian model)	
ML based global sigma estimate:	4.202616
Unbiased global sigma estimate:	4.207160
-2 log-likelihood:	31732.241354
Classic AIC:	31758.241354
AICc:	31758.307010
BIC/MDL:	31844.340270
CV:	17.864078
R square:	0.054463
Adjusted R square:	0.052417

Variable	Estimate	Standard Error	t(Est/SE)
Intercept	8.440770	0.887355	9.512286
TR_protopo	-9.536042	3.755792	-2.539023
TR_proto_1	602.148818	724.540716	0.831077
twowheel	1.113778	0.201770	5.520044
fourwheel	-0.355032	0.160463	-2.212550
giant	-3.068034	1.988361	-1.542997
SO_RAZDEP	0.017980	0.014053	1.279374
SO_T_ENV	-0.297256	0.032315	-9.198565
SO_GINI	3.137685	1.086014	2.889175
SO_T_DENS	-0.011601	0.009385	-1.236059
SO_T_OCUPD	-0.077744	0.045718	-1.700513
SO_I_ESCOL	-3.361244	0.749987	-4.481737

b

GWR (Geographically weighted regression) result

****

Bandwidth and geographic ranges

Bandwidth size: 273.852127

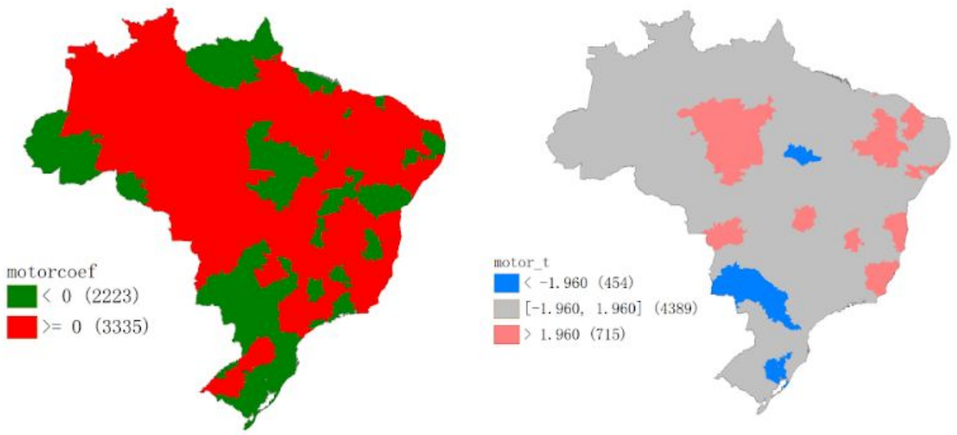
Coordinate	Min	Max	Range
X-coord	-73.089956	-34.826007	38.263950
Y-coord	-33.689565	4.621500	38.311065

Diagnostic information

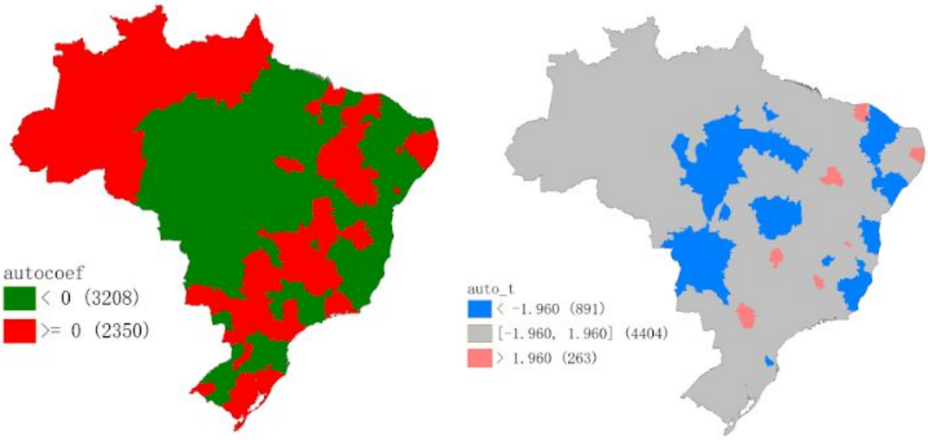
Residual sum of squares:	52158.683167
Effective number of parameters (model: trace(S)):	553.938155
Effective number of parameters (variance: trace(S'S)):	381.589043
Degree of freedom (model: n - trace(S)):	5004.061845
Degree of freedom (residual: n - 2trace(S) + trace(S'S)):	4831.712734
ML based sigma estimate:	3.063402
Unbiased sigma estimate:	3.285585
-2 log-likelihood:	28217.573634
Classic AIC:	29327.449943
AICc:	29450.803594
BIC/MDL:	33002.801796
CV:	15.374074
R square:	0.497603
Adjusted R square:	0.422069

Figure 5. Regression results about the association between TBI mortality rate and socioeconomic, demographic and health care variables. a) results from ordinary least squares regression b) results from geographically weighted regression

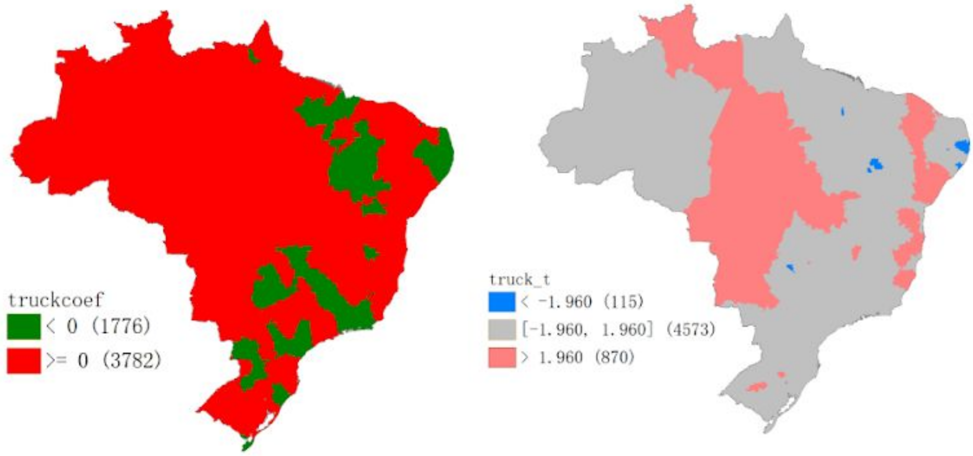
a



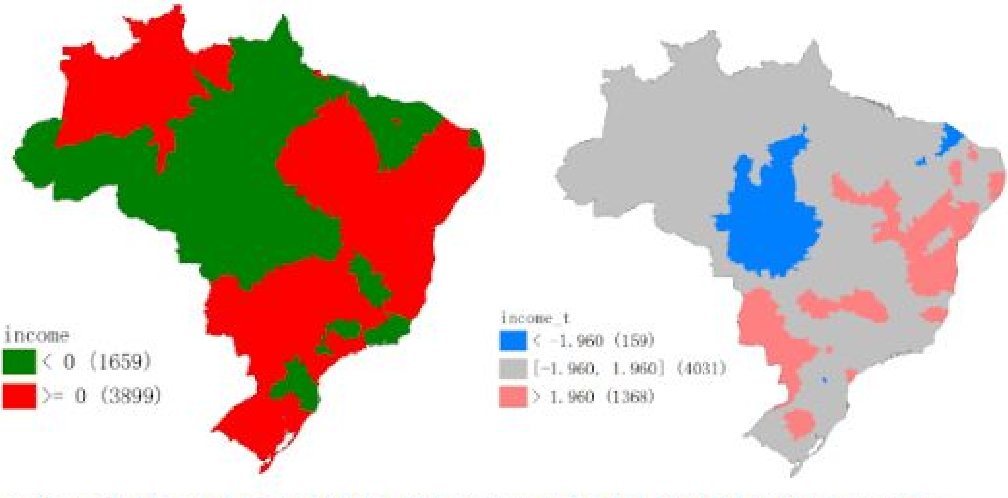
b


autocoef
< 0 (3208)
>= 0 (2350)
auto_t
< -1.960 (891)
[-1.960, 1.960] (4404)
> 1.960 (263)

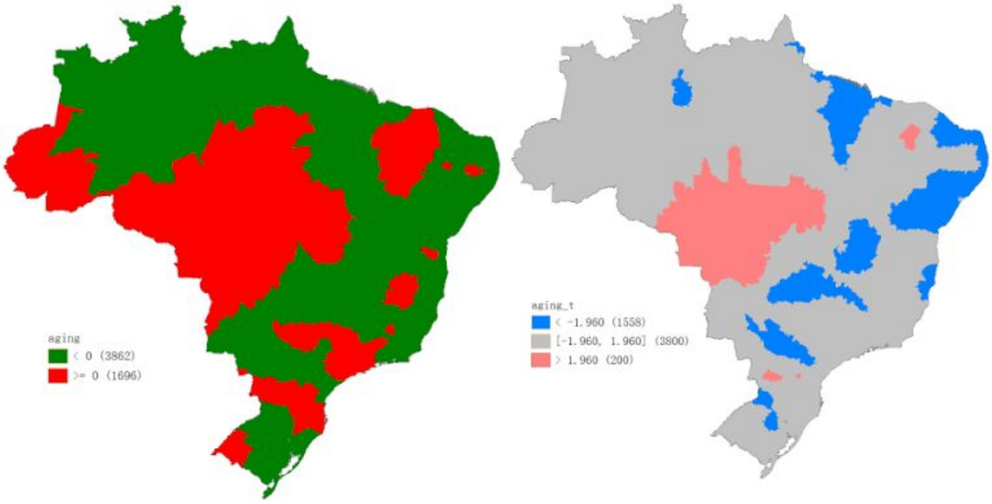
c


truckcoef
< 0 (1776)
>= 0 (3782)
truck_t
< -1.960 (115)
[-1.960, 1.960] (4573)
> 1.960 (870)

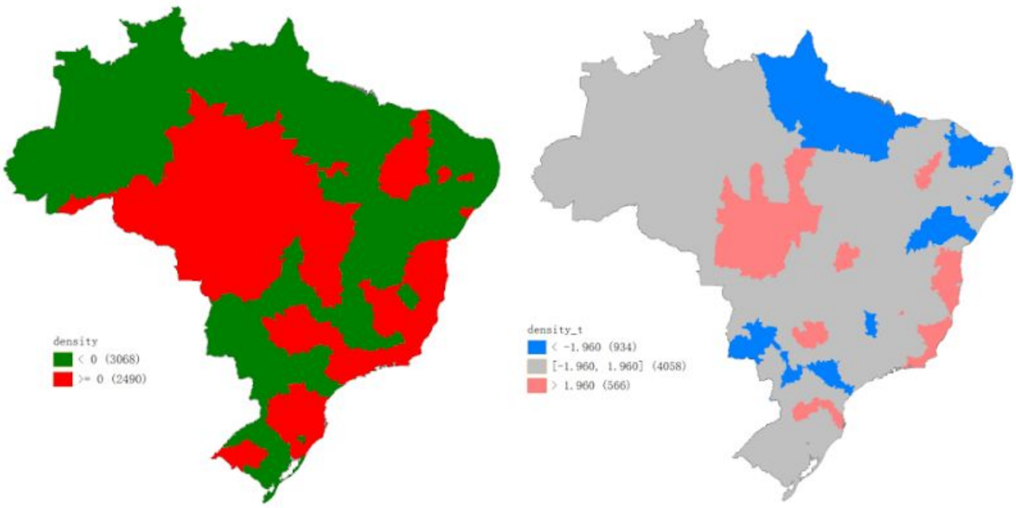
d


income
< 0 (1659)
>= 0 (3899)
income_t
< -1.960 (159)
[-1.960, 1.960] (4031)
> 1.960 (1368)

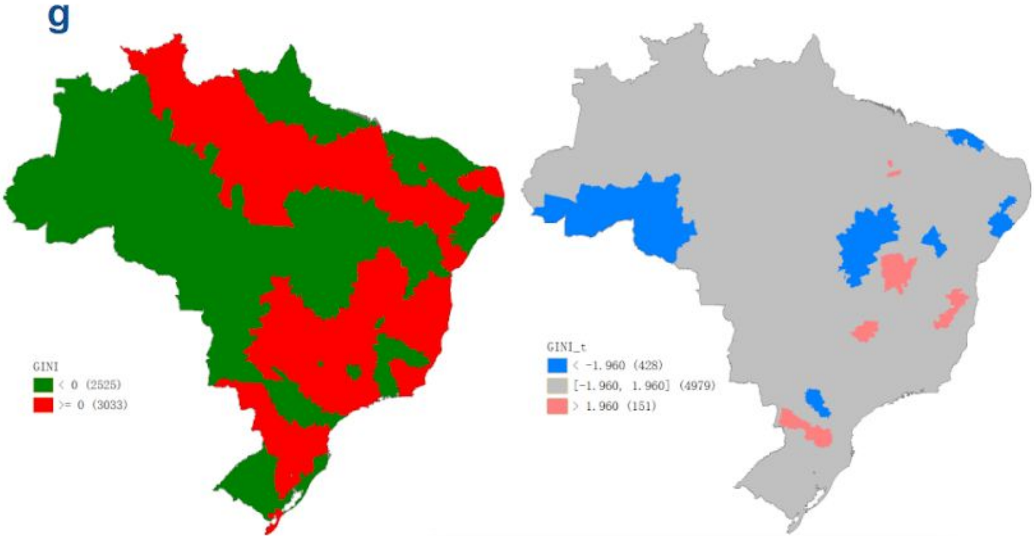
e


aging
< 0 (3862)
>= 0 (1696)
aging_t
< -1.960 (1558)
[-1.960, 1.960] (3800)
> 1.960 (200)

f


density
< 0 (3068)
>= 0 (2490)
density_t
< -1.960 (934)
[-1.960, 1.960] (4058)
> 1.960 (566)

g


GINI
< 0 (2525)
>= 0 (3033)
GINI_t
< -1.960 (428)
[-1.960, 1.960] (4979)
> 1.960 (151)

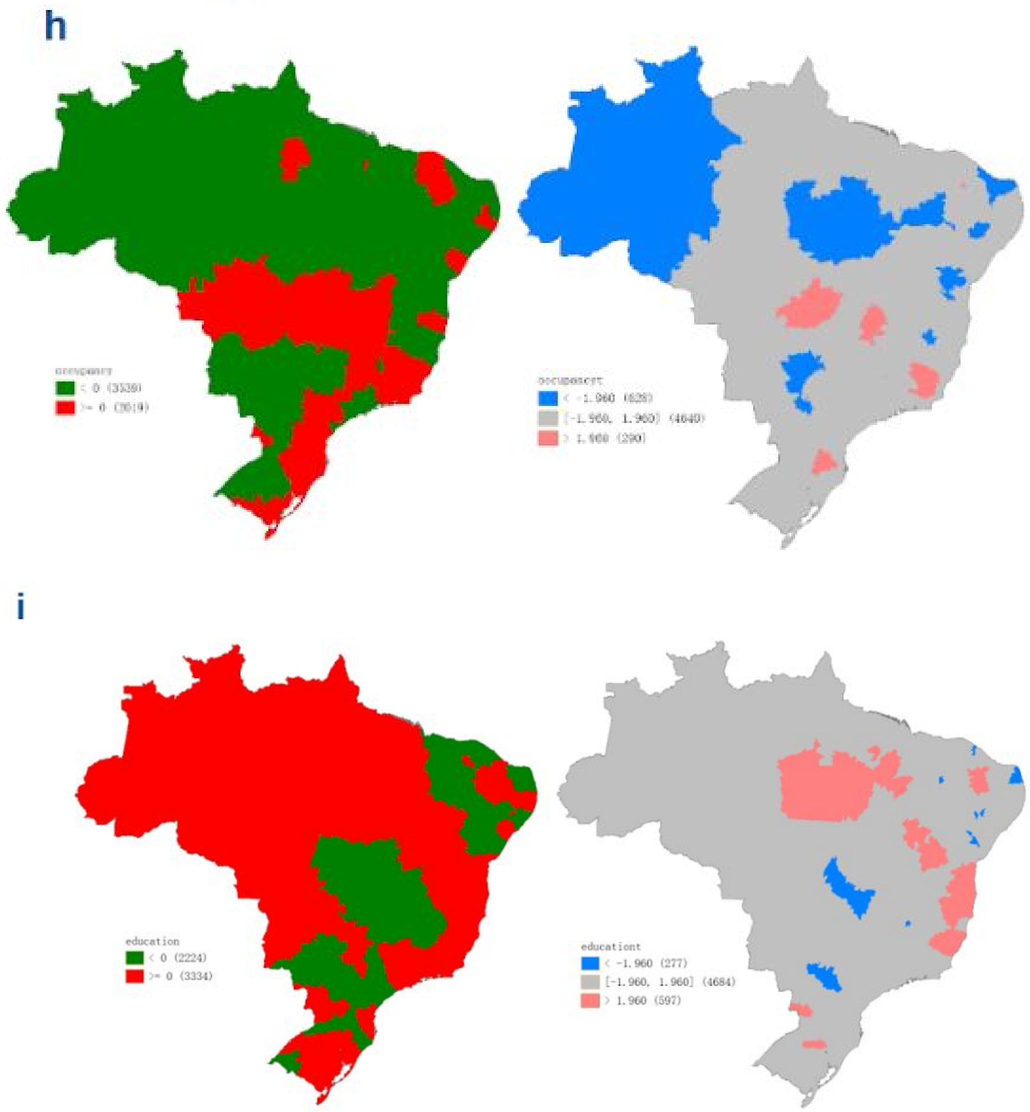


Figure 6. Visualization of the distribution of beta coefficient and t-value for socio economics and demographics. (a) motorcycles. (b) automobiles. (c) giant vehicles. (d) income ratio. (e) aging rate. (f) density ratio. (g) Gini index. (h) occupancy and displacement rate. (i) education attainment.

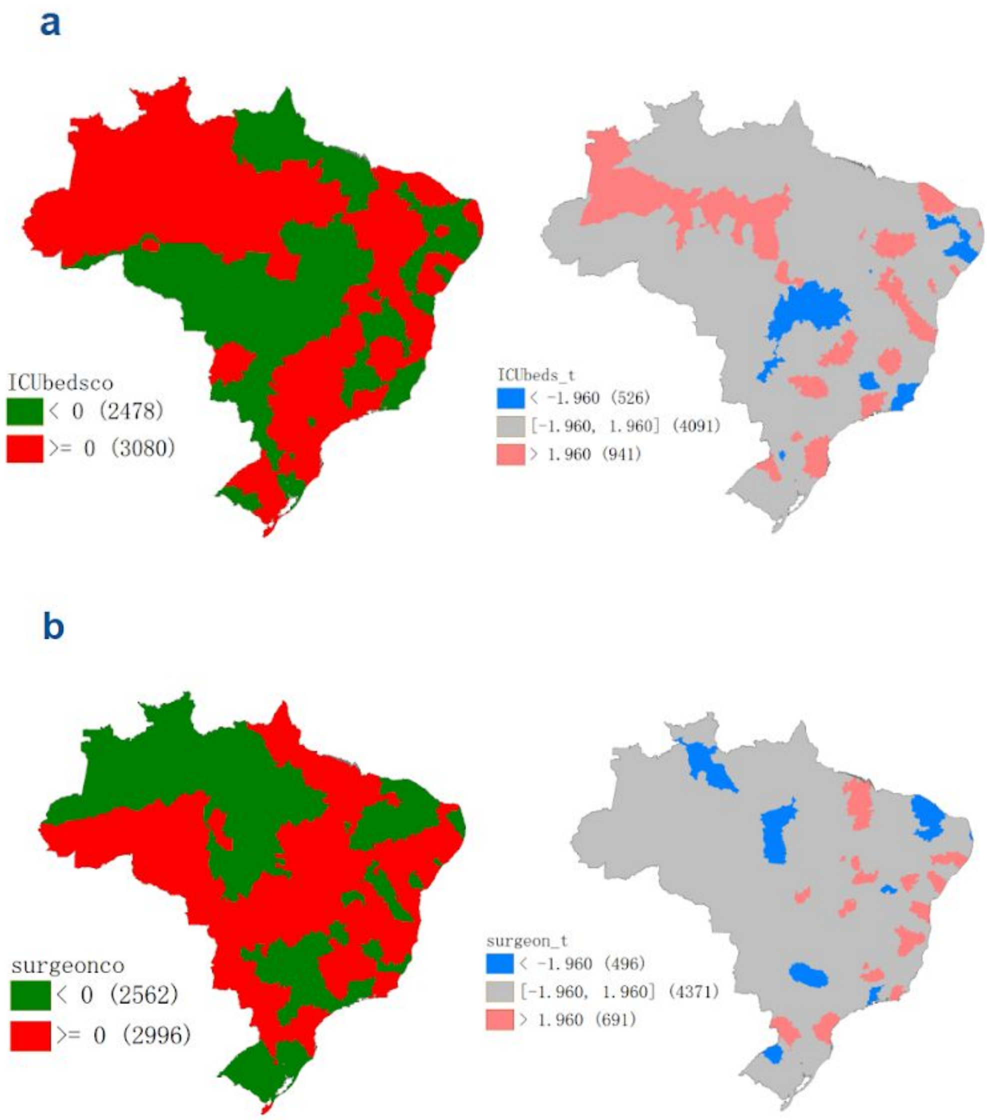


Figure 7. Visualization of the distribution of beta coefficient and t-value for health care. (a) accessibility to ICU beds. (b) accessibility to neurosurgeons.

3.2 TBI prognostic model

3.2.1 TBI patient profile

For both datasets, patients had mean age between 30 to 40 years old and the majority (>80%) were male patients. Among all the 752 Brazilian TBI patients, 109(14.49%) patients had poor prognosis while 634 (85.51%) patients had good prognosis. Age, alcohol assumption, AVPU scale score, disposition from emergency department, whether go from surgery ward to ICU, received TBI surgery, received other surgery, pupil reaction, pulse oxygen and total Glasgow Coma Score are significantly different between these two groups. While for Tanzanian patients, 555 (14.01%) patients had poor prognosis while 3406 (85.99%) patients had good prognosis. More variables are significantly different between patients with good outcomes and bad outcomes, which includes age, mechanism of injury, alcohol assumption, AVPU scale result, disposition from emergency department, whether go from surgery ward to ICU, pupil reaction, respiratory rate, pulse, pulse oxygen and total Glasgow Coma Score.

In both datasets, patients with good outcome had mean age around 30 while patients with poor outcome had mean age around 35. For Brazilian patients, 336 (52.26%) patients with good outcome had no alcohol assumption while 41(37.61%) patients with poor outcome had no alcohol assumption. For the AVPU scale result, 550 (85.54%) patients in the good recovery group remained alert while 30 (27.52%) patients in the poor recovery group remained alert. Furthermore, more patients with good recovery had higher levels of pupil reactivity, pulse oxygen and total Glasgow Coma Score. However, patients with poor outcomes were mostly those who were disposed of in the ICU from the emergency department and those who were sent from the surgery ward to ICU. While for Tanzanian patients, 2258 (66.29%) patients with good outcome while 404 (72.79%) patients with poor outcome were involved in road traffic injury. 1724 (50.62%) patients with good outcome while 213 (38.38%) patients with poor outcome had no alcohol use. 2918 (85.67%) patients with good outcome while 147 (26.49%) patients with poor outcome remained alert for the AVPU scale test. 80 (14.41%) patients with poor outcome while 36 (1.06%) patients were disposed from the Emergency Department to ICU. Compared to patients with good outcome, patients with poor outcome were more likely to have TBI surgery, be transferred from surgical ward to ICU, had weaker pupil reaction, have lower level of pulse oxygen and total Glasgow Coma Score.

Table 1 - Brazilian Patient Profile

	Total	Poor Outcome	Good Outcome	p-value
n	752	109	643	
Age, mean(sd)	32.27 (16.96)	37.18(19.67)	31.44 (16.32)	0.005
Gender				0.392
female, n(%)	121(16.09)	14(12.84)	107(16.64)	
male, n(%)	631(83.91)	95(87.16)	536(83.36)	
Mechanism of Injury				0.012
road traffic injury, n(%)	495(65.82)	78(71.56)	417(64.85)	
assault, n(%)	92(12.23)	4(3.67)	88(13.69)	
fall, n(%)	83(11.04)	17(15.60)	66(10.26)	
other, n(%)	82(10.90)	10(9.17)	72(11.20)	
Alcohol				<0.001
no, n(%)	377(50.13)	41(37.61)	336(52.26)	
yes, n(%)	243(32.31)	34(31.19)	209(32.50)	
unknown, n(%)	132(17.55)	34(31.19)	98(15.24)	
AVPU				<0.001
alert, n(%)	580(77.13)	30(27.52)	550(85.54)	
respond to verbal, n(%)	26(3.46)	2(1.83)	24(3.73)	
respond to pain, n(%)	112(14.89)	45(41.28)	67(10.42)	
unresponsive, n(%)	34(4.52)	32(29.36)	2(0.31)	
Disposition from the Emergency Department				<0.001
ICU, n(%)	26(3.46)	18(16.51)	8(1.24)	
surgery ward, n(%)	646(85.90)	87(79.82)	559(86.94)	
OT, n(%)	5(0.66)	1(0.92)	4(0.62)	
death, n(%)	4(0.53)	3(2.75)	1(0.16)	
home, n(%)	71(9.44)	0(0)	71(11.04)	
TBI Surgery				1
no, n(%)	533(70.88)	77(70.64)	456(70.92)	
yes, n(%)	219(29.12)	32(29.36)	187(29.08)	

Other Surgery				0.199
no, n(%)	627(83.38)	96(88.07)	531(82.58)	
yes, n(%)	125(16.62)	13(11.93)	112(17.42)	
Surgical Ward to ICU				<0.001
no, n(%)	614(81.65)	52(47.71)	562(87.40)	
yes, n(%)	138(18.35)	57(52.29)	81(12.60)	
Pupils				<0.001
bilateral Reactive, n(%)	715(95.08)	79(72.48)	636(98.91)	
unilateral Reactive, n(%)	16(2.13)	13(11.93)	3(0.47)	
nonreactive, n(%)	21(2.79)	17(15.60)	4(0.62)	
Vital Signs				
temperature, mean(sd)	36.40(0.76)	36.56(1.06)	36.37(0.70)	0.070
respiratory rate, mean(sd)	21,73(5.30)	22.19(4.28)	21.65(5.45)	0.247
pulse, mean(sd)	89.46(18.47)	90.54(22.40)	89.27(17.74)	0.575
systolic blood pressure, mean(sd)	122.87(23.01)	120.92(32.85)	123.20(20.91)	0.484
diastolic blood pressure, mean(sd)	72.83(15.59)	70.92(17.92)	73.16(15.15)	0.220
pulse oxygen, mean(sd)	94.87(8.55)	89.37(14.25)	95.81(6.64)	<0.001
Clinical Exam				
gcs_total, mean(sd)	13.26(3.29)	8.47(4.41)	14.07(2.19)	<0.001

Table 2 - Tanzanian Patient Profile

	Total	**Poor Outcome**	**Good Outcome**	**p-value**
n	3961	555	3406	
Age, mean(sd)	32.06(16.65)	35.45(17.89)	31.45 (16.40)	<0.001
Gender				
female, n(%)	691(17.45)	83(14.95)	608(17.85)	0.1081
male, n(%)	3270(82.55)	472(85.05)	2798(82.15)	
Mechanism of Injury				<0.001
road traffic injury, n(%)	2662(67.21)	404(72.79)	2258(66.29)	
assault, n(%)	561(14.16)	39(7.03)	522(15.33)	
drowning, n(%)	3(0.08)	1(0.18)	2(0.06)	
fall, n(%)	425(10.73)	80(14.41)	345(10.13)	

other, n(%)	310(7.83)	31(5.59)	279(8.19)	
Alcohol				<0.001
no, n(%)	1937(48.90)	213(38.38)	1724(50.62)	
yes, n(%)	1059(26.74)	148(26.67)	911(26.75)	
unknown, n(%)	965(24.36)	194(34.95)	771(22.64)	
AVPU				<0.001
alert, n(%)	3065(77.38)	147(26.49)	2918(85.67)	
respond to verbal, n(%)	149(3.76)	20(3.60)	129(3.79)	
respond to pain, n(%)	548(13.83)	222(40.00)	326(9.57)	
unresponsive, n(%)	199(5.02)	166(29.91)	33(0.97)	
Disposition from the Emergency Department				<0.001
ICU, n(%)	116(2.93)	80(14.41)	36(1.06)	
surgery ward, n(%)	3397(85.76)	442(79.64)	2955(86.76)	
OT, n(%)	20(5.05)	4(0.72)	16(0.47)	
death, n(%)	30(0.76)	28(5.05)	2(0.06)	
home, n(%)	398(10.05)	1(0.18)	397(11.66)	
TBI Surgery				<0.001
no, n(%)	2685(67.79)	370(66.67)	2315(67.97)	
yes, n(%)	915(23.10)	182(32.79)	733(21.52)	
unknown, n(%)	361(9.11)	3(0.54)	358(10.51)	
Other Surgery				<0.001
no, n(%)	3078(77.71)	476(85.77)	2602(76.39)	
yes, n(%)	513(12.95)	77(13.87)	436(12.80)	
unknown, n(%)	370(9.34)	2(0.36)	368(10.80)	
Surgical Ward to ICU				<0.001
no, n(%)	2962(74.78)	239(43.06)	2723(79.95)	
yes, n(%)	999(25.22)	316(56.94)	683(20.05)	
unknown, n(%)	0(0)	0(0)	0(0)	
Pupils				<0.001
bilateral Reactive, n(%)	3752(94.72)	395(71.17)	3357(98.56)	
unilateral Reactive, n(%)	90(2.27)	66(11.89)	24(0.70)	
nonreactive, n(%)	109(2.75)	91(16.40)	18(0.53)	
unknown, n(%)	9(0.23)	2(0.36)	7(0.21)	
Vital Signs				
temperature, mean(sd)	36.44(0.73)	36.50(1.02)	36.44(0.68)	0.1536

respiratory rate, mean(sd)	21.79(4.76)	22.60(5.65)	21.66(4.59)	<0.001
pulse, mean(sd)	88.17(18.10)	91.25(23.53)	87.67(17.00)	<0.001
systolic blood pressure, mean(sd)	122.01(21.73)	121.59(27.91)	122.08(20.55)	0.6908
diastolic blood pressure, mean(sd)	72.90(15.62)	71.46(17.94)	73.13(15.20)	0.03798
pulse oxygen, mean(sd)	95.34(7.66)	89.33(14.69)	96.32(5.13)	<0.001
Clinical Exam				
gcs_total, mean(sd)	13.24(3.26)	8.56(4.39)	14.00(2.26)	<0.001

3.2.2 TBI models performance

We tested eight machine learning models using three different training strategies. The models trained by combined datasets outperformed other models. The value of AUC varies from 79.9% (K nearest neighbors) to 92.3% (Random Forest) trained by Tanzanian-Brazilian datasets. Most models have similar values of AUC around 89%, among which Random Forest had the strongest classification capability with largest AUC value and 95% confidence interval of AUC from 91.75% to 91.4%. Additionally, the model also has strong classification parameters: sensitivity (0.92), specificity (0.77), positive predictive value (0.96), negative predictive value (0.61) and accuracy (0.90). The model performed better to discriminate against poor TBI outcomes than good TBI outcomes.

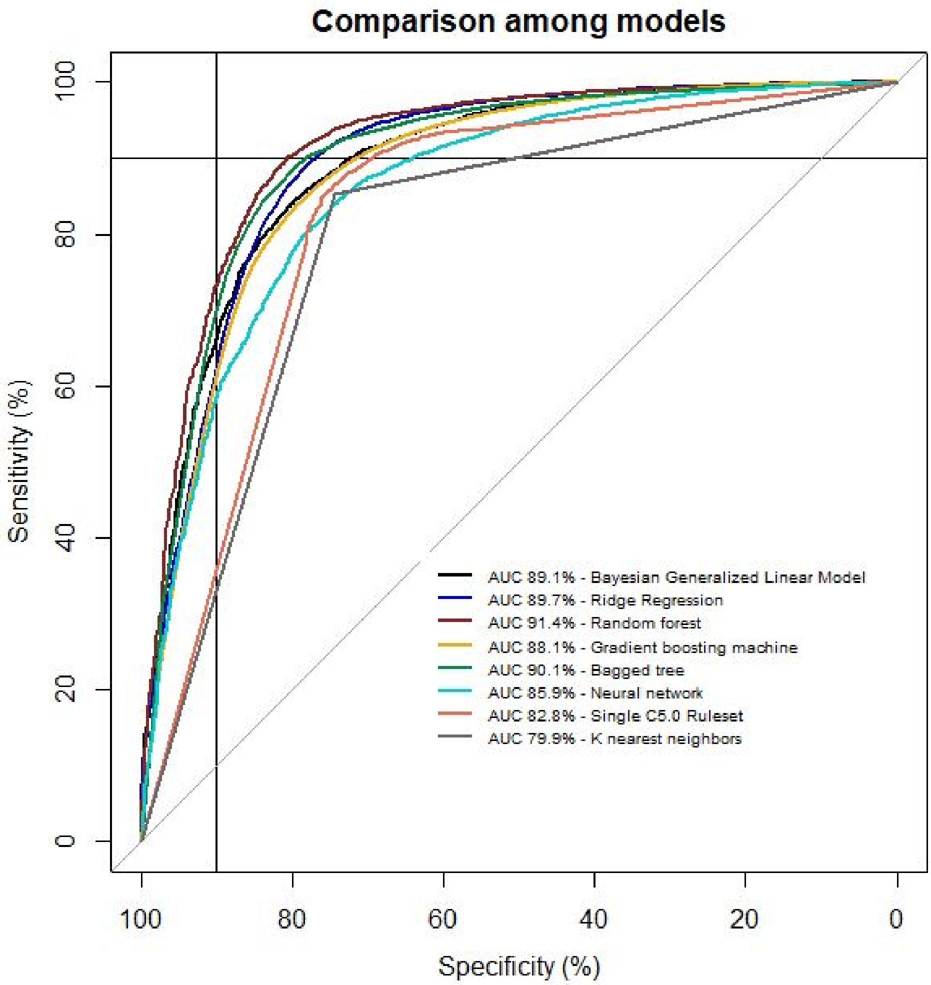


Figure 8 - Comparison between AUC of eight machine learning models trained by Tanzanian-Brazilian datasets.

On the other hand, the value of AUC was relatively lower for models trained by Brazilian dataset alone, which ranged from 74.20% (K nearest neighbors) to 88.00% (Bayesian Generalized Linear Model). The value of AUC was the smallest for models trained by Tanzanian dataset and tested by Brazilian dataset. The optimum model under this scenario was the Bayesian Generalized Linear Model with AUC of 86.2%.

Table 3 - comparison between AUC of machine learning models trained by Tanzanian dataset and Brazilian dataset separately

	Tanzanian-Brazilian-combined-based model	Tanzania-based model predicting Brazil data	Brazilian-based model
knn (k-Nearest Neighbor)	79.9% (79.68%, 80.03%)		74.2% (73.81%, 74.64%)
ridge (Ridge Regression)	89.7% (89.37%, 89.98%)		87.7% (87.03%, 88.3%)
bag_fit (bagged tree)	90.1% (89.41%, 90.84%)		83.5% (81.42%, 85.49%)
bayes_fit (Bayesian Generalized Linear Model)	89.1% (88.42%, 89.86%)	86.2% (85.32%, 87.14%)	88.0% (86.39%, 89.71%)
c5_fit (Single C5.0 Ruleset)	82.8% (81.86%, 83.68%)		80.3% (78.14%, 82.43%)
nnFit (Neural Network)	85.9% (85.14%, 86.75%)		
gbm_Fit (Gradient Boosting Machines)	88.1% (87.95%, 88.23%)		85.2% (84.84%, 85.56%)
rfFit (Random Forest)	91.4% (90.73%, 92.05%)		87.5% (85.72%, 89.25%)

4. Discussion

4.1 five-year TBI mortality

To our knowledge, this is the first national evaluation of TBI mortality rates and its attributable risk factors in Brazil. Local clusters of cities with high TBI mortality are identified in central-west, southeast and northeast regions of the country. The causes of higher rates in these regions are varied and likely compounded. These regions have more motorcycles and trucks, larger inequality in income distribution, denser population, as well as limited healthcare accessibility.

Our study provides enlightenment for evidence-based policy on reduction of TBI mortality in Brazil. The data indicates prevalence of vehicles and types of vehicles used can increase TBI fatalities. This impact could appear in the setting of poor safety regulations and a lack of education on road safety, as well as poor enforcement of traffic rules. Road traffic injuries prevalence is not only related to increases in vehicles, but also the type of vehicle involved (Gedeborg et al, 2010). Brazilian cities have entered into the "urban mobility crisis" since 2012 (Rodrigues, 2012). In 2012, 3.418 million cars were produced in Brazil, making it the seventh-leading producer of automotives. From our data, the central-west, northeast and southeast regions had higher distribution of two-wheel vehicles. While motorcycles are cheaper and more affordable for developing regions, their riders have a 34-fold higher risk of death in a crash than riders of other types of vehicles per mile traveled. More strict road regulations and rules as well as education on road safety should be enforced.

Additionally, management of TBI requires both acute and critical healthcare facilities which are limited or lacking in low and middle-income countries. Given TBI management requires advanced care, we chose accessibility to ICU beds and neurosurgeons as surrogates for strengthening the health system in the region. Our data found partial southeast, south regions and northeast regions have access to ICU beds and partial southeast, south, northeast and central-west regions have access to neurosurgeons while other regions are with limited, or even no accessibility to ICU beds and neurosurgeons. Accessibility to health care could significantly reduce TBI mortality in partial northeast, southeast and central-west and south regions. However, even those regions which can get access to health care, the health care coverage is not enough. The lack of health resources could be due to limitations in government funding. Unequal and fluctuating federal funding prevents those regions from developing necessary health systems to meet healthcare needs for a dense population. However, our analysis only evaluates the accessibility to ICU beds and neurosurgeons, but doesn't evaluate the equipment, or transfer resources which also have a significant impact on TBI treatment. Additionally, our study also finds accessibility to health care can significantly increase TBI mortality in partial south, south and northeast regions. This is because more severe TBI patients are sent to these places to seek health care. Since the healthcare system in Brazil is operated through a referral process, delayed healthcare happens in regions with highly dense populations due to limited capacity of medical professionals and equipment, which leads to poor TBI outcomes like mortality in these places. Therefore, health ministry funding should be allocated to the construction of healthcare facilities and personnels to meet the capacity for TBI management.

4.2 TBI prognostic model

Results showed that all the three training strategies of using Brazilian dataset alone, Tanzanian dataset alone and combined Brazilian-Tanzanian dataset developed prognostic models successfully that predict in-hospital TBI outcome. Most models had over 80% probability to make correct classification of TBI prognosis, which implies the feasibility to apply machine learning techniques to clinical decision support systems.

The optimum model in our study was developed by training with Tanzanian-Brazilian dataset, which indicated the possibility of establishing a generalized TBI prognostic model for low- and middle-income countries using multinational datasets. These countries shared similarity in clinical settings, which make it feasible to use similar input predictors for training, such as casualty department disposition. The application of the TBI prognostic model could help relieve the burden of limited medical resources and delayed health care in low- and middle-income countries.

However, the quality of the data plays an indispensable role in building up the predictive models. Random Forest developed by the combined dataset showed strong classification capability. There were 3873 observations with 24 variables for Tanzanian-Brazilian dataset after data cleaning. The important predictors for poor TBI outcome from the model are glasgow coma score, AVPU, transition from surgery and pulse oxygen.

On the other hand, Brazilian dataset is much smaller with only 752 observations. After data cleaning, there were 22 variables left as input predictors for model training. As a result, the models learnt from much less data and predicted outcomes less accurately than those trained by larger dataset with more input predictors.

Furthermore, for models trained by Tanzanian dataset and tested by Brazilian dataset, despite larger data in Tanzanian dataset, we compared and used the same input predictors from two datasets. Therefore, we removed inconsistent variables which made the training dataset maintained even less variables and negatively impact the classification capability of the models.

4.3 Study strengths and limitations

4.3.1 TBI mortality

Our study has several limitations. First, we do not know the mechanism (fall, traffic, guns, fights, etc) of TBI for each patient or where it occurred (on the road, in the city, at work, or at home). Second, we were not able to find references regarding Brazilian government investment in public health by cities. Finally, we analyzed health care system infrastructure only by the accessibility to ICU beds and neurosurgeons, but didn't evaluate the equipment, or transfer resources which are indispensable to the prognosis of TBI. The treatment of TBI requires both surgical and non-surgical healthcare.

4.3.2 TBI prognostic model

One of the limitations is that the Brazilian dataset is small with only 752 observations. As a result, there exists imbalance in the composition of combined dataset and limited variables for Brazilian dataset after data cleaning, which might impact the predictive capability of the models. Our next step is to collect patient data from five more hospitals in Brazil and merge all the datasets together to improve the present TBI prognostic model.

Additionally, in our study, some models may not be ideal in some scenarios, for example, neural networks do not perform well for small dataset. Therefore, more classification models for binomial classification need to be tested to find the optimum algorithm.

5. Conclusion

Overall, TBI mortality is a severe public health problem in Brazil that exerts heavy burden on the society and impedes the economic development of the country. Given the high prevalence of TBI mortality, evidence-based policies are urgent to reduce TBI mortality on enforcement of strict road regulation and rules, safety education coverage, construction of healthcare infrastructure, training of medical professionals as well as minimizing the inequality in income.

Furthermore, the established TBI prognostic model implies the feasibility of developing a generalized TBI prognostic model for LMICs, which helps timely diagnosis and medical treatment. Therefore, it would help solve problems of delayed health care, reduce TBI mortality and relieve the burden of limited medical resources. Next steps are collecting data from multiple countries and testing more classification models to further improve the performance of the generalized model.

References

1. Hyder, A. A., Wunderlich, C. A., Puvanachandra, P., Gururaj, G., & Kobusingye, O. C. (2007). The impact of traumatic brain injuries: A global perspective. NeuroRehabilitation, 22(5), 341–353. https://doi.org/10.3233/NRE-2007-22502

2. Langlois JA, Rutland-Brown W, & Wald MM. (2006). The Epidemiology and Impact of Traumatic Brain Injury. J Head Trauma Rehabil, 21(5), 275-378.

3. Liao, C. C., Chiu, W. T., Yeh, C. C., Chang, H. C., & Chen, T. L. (2012). Risk and outcomes for traumatic brain injury in patients with mental disorders.Journal of Neurology, Neurosurgery & Psychiatry, 83(12), 1186-1192.

4. Shao, J., Zhu, H., Yao, H., Stallones, L., Yeates, K., Wheeler, K., & Xiang, H. (2012). Characteristics and Trends of Pediatric Traumatic Brain Injuries Treated at a Large Pediatric Medical Center in China, 2002–2011. PLoS ONE, 7(12), e51634. https://doi.org/10.1371/journal.pone.0051634

5.Harrison, D. A., Prabhu, G., Grieve, R., Harvey, S. E., Sadique, M. Z., Gomes, M., ... & Rowan, K. M. (2013). Risk adjustment In neurocritical care (RaIn)–prospective validation of risk prediction models for adult patients with acute traumatic brain injury to use to evaluate the optimum location and comparative costs of neurocritical care: a cohort study.

6. Jourdan, C., Bosserelle, V., Azerad, S., Ghout, I., Bayen, E., Aegerter, P., ... & Azouvi, P. (2013). Predictive factors for 1-year outcome of a cohort of patients with severe traumatic brain injury (TBI): results from the PariS-TBI study. Brain injury, 27(9), 1000-1007.

7. Roozenbeek, B., Maas, A. I., & Menon, D. K. (2013). Changing patterns in the epidemiology of traumatic brain injury. Nature Reviews Neurology, 9(4), 231-236.

8. Walder, B., Haller, G., Rebetez, M. M. L., Delhumeau, C., Bottequin, E., Schoettker, P., ... & Osterwalder, J. (2013). Severe traumatic brain injury in a high-income country: An epidemiological study. Journal of neurotrauma,30(23), 1934-1942.

9. Khan, A., Prince, M., Brayne, C., & Prina, A. M. (2015). Lifetime prevalence and factors associated with head injury among older people in low and middle income countries: a 10/66 study. PloS one, 10(7), e0132229.

10. Ceriani, L., & Verme, P. (2012). The origins of the Gini index: Extracts from Variabilità e Mutabilità (1912) by Corrado Gini. The Journal of Economic Inequality, 10(3), 421–443. https://doi.org/10.1007/s10888-011-9188-x

11.Paim J, Travassos C, Almeida C, Bahia L, Macinko J. The Brazilian health system: history, advances, and challenges. Lancet. 2011;377(9779):1778-97.

12. Azzoni, C. R. (2001). Economic growth and regional income inequality in Brazil. The annals of regional science, 35(1), 133-152.

13. Garcia-Subirats, I., Vargas, I., Mogollon-Perez, A. S., De Paepe, P., da Silva, M. R., Unger, J. P., . . . Vazquez, M. L. (2014). Inequities in access to health care in different health systems: a study in municipalities of central Colombia and north-eastern Brazil. Int J Equity Health, 13(1), 10. doi:10.1186/1475-9276-13-10

14. da Silva, Z. P., Ribeiro, M., Barata, R. B., & de Almeida, M. F. (2011). Socio-demographic profile and utilization patterns of the public healthcare system (SUS), 2003-2008. Cien Saude Colet, 16(9), 3807-3816.

15. Viacava, F., & Bellido, J. G. (2016). Health, access to services and sources of payment, according to household surveys. Ciencia & saude coletiva, 21(2), 351-370.

16. [Main causes of head trauma in the city of Salvador, Bahia, Brazil] Most frequent causes of head injury in the City of Salvador, Bahia, Brazil. (n.d.). Retrieved March 9, 2020, from http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&src=google&base=LILACS&lang=p&nextAction=lnk&exprSearch=435408&indexSearch=ID

17. Cranioencephalic trauma: Correlation between demographic data, Glasgow scale ... (n.d.). Retrieved March 9, 2020, from https://teses.usp.br/teses/disponiveis/5/5151/tde-21062007-145931/en.php

18. Almeida, C. E. R. de, Fiho, J. L. S., Dourado, J. C., Gontijo, P. A. M., Dellaretti, M. A., Costa, B. S. (2016). Traumatic Brain Injury Epidemiology in Brazil. World Neurosurgery, 87, 540-547. https://doi.org/10.1016/j.wneu.2015.10.020

19. Faria, J. W. V. de, Nishioka, S. de A., Arbex, G. L., Alarcão, G. G., & Freitas, W. B. de. (2008). Occurrence of severe and moderate traumatic brain injury in patients attended in a Brazilian Teaching Hospital: Epidemiology and dosage of alcoholemy. Arquivos de Neuro-Psiquiatria, 66(1), 69–73. https://doi.org/10.1590/S0004-282X2008000100016

20. Ramos, E. M. S., Silva, M. K. B. da, Siqueira, G. R. de, Vieira, R. A. G., & França, W. L. C. (2010). Aspectos epidemiológicos dos traumatismos cranioencefálicos atendidos no Hospital. Revista Brasileira Em Promoção Da Saúde, 23(1), 4–10. https://doi.org/10.5020/18061230.2010.p4

21.MOURA, A. C. M.. Geoprocessamento na gestão e planejamento urbano. Belo Horizonte: Ed. Da autora, 2003, 294p.

22. Martins, E. T., Silva, T. D., & Coutinho, M. (2003). Estudo de 596 casos consecutivos de traumatismo craniano grave em Florianópolis-1994-2001.Rev Bras Ter Intensiva, 15(1), 15-8.

23. Maeda, Y., Ichikawa, R., Misawa, J., Shibuya, A., Hishiki, T., Maeda, T., Yoshino, A., & Kondo, Y. (2019). External validation of the TRISS, CRASH, and IMPACT prognostic models in severe traumatic brain injury in Japan. PLOS ONE, 14(8), e0221791. https://doi.org/10.1371/journal.pone.0221791

24. Perel, P., Edwards, P., Wentz, R. & Roberts, I. Systematic review of prognostic models in traumatic brain injury. BMC Medical Informatics and Decision Making 6, (2006).

25. Signorini, D., Andrews, P., Jones, P., Wardlaw, J., & Miller, J. (1999). Predicting survival using simple clinical variables: A case study in traumatic brain injury. Journal of Neurology, Neurosurgery, and Psychiatry, 66(1), 20–25.

26. Li, Y.-C., Liu, L., Chiu, W.-T., & Jian, W.-S. (2000). Neural network modeling for surgical decisions on traumatic brain injury patients. International Journal of Medical Informatics, 57(1), 1–9. https://doi.org/10.1016/S1386-5056(99)00054-4