The Impact of Care Delays on Traumatic Brain Injury Outcomes in Tanzania: Descriptive Analytics and Machine Learning

by

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Lawrence Park

Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute
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ABSTRACT

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Abstract

Background: Traumatic brain injury (TBI) is the leading cause of trauma related death and disability worldwide. Poor TBI outcomes disproportionately affect low- and middle-income countries (LMICs). Treatment delays may contribute to poor TBI outcomes in LMIC emergency departments (EDs). A prognostic model is a low-cost, user-friendly solution to optimizing patient care in low-resource hospitals. The aim of this study was twofold: (1) assess associations between care delays and TBI patient outcomes, and (2) build a prognostic model that uses care delays to predict TBI patient outcomes.

Methods: This study uses a 3209 de-identified TBI patient registry from Kilimanjaro Christian Medical Center (KCMC) ED in Moshi, Tanzania. We created nine variables representing delays to care and assessed their association with poor outcomes (Glasgow Coma Score (GCS) < 4) using logistic regression. We then constructed a prognostic model that predicts TBI patient outcomes dichotomized as good (GCS ≥ 4) and poor (GCS < 4). Predictors included socio-demographics, injury characteristics, vital signs, and care delays.

Results: Associations between care delays and TBI outcomes were not significant. However, care delays were top predictors of a poor outcome in our prognostic model. Our model achieved an area under the receiver operating curve of 89.5% (95% CI: 88.8, 90.3).

Conclusion: Our TBI prognostic model demonstrates the predictive value of care delay information. Time to care data is easy to collect. A prognostic model that uses time to

care data allows healthcare providers to update patient prognosis as patients progress through their hospital stay.

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1. Introduction

Traumatic brain injury (TBI) is the leading cause of trauma related death and disability worldwide, with an estimated 69 million occurrences each year (Dewan et al., 2018; Rubiano et al., 2015). The global burden of TBI falls disproportionately on low- and middle-income countries (LMICs) which account for 90% of all injury related deaths and 72% of all TBIs (WHO Injuries and Violence: the Facts, 2014; Rubiano et al., 2015; Dewan et al., 2018). Among LMICs, one of the largest TBI rates occurs in the sub-Saharan region of Africa which experiences 359 TBI cases per 100,000 people per year (Hyder et al., 2007). For comparison, the global TBI incidence is 193 cases per 100,000 people per year (Hyder et al., 2007). Unfortunately, future projections estimate up to 14 million additional TBI cases per year on the African continent (Wong et al., 2016).

The significant burden of TBI in sub-Saharan Africa has been attributed to a rapid growth in motor vehicle use without an equally swift expansion in road development and traffic safety mechanisms (Haagsma et al., 2016; Diamond et al., 2018). The result of this infrastructural lag behind changing human behavior has been an increase in road traffic accidents and therefore an increase in TBIs (Murray et al., 2012). In 2016, the Africa World Health Organization (WHO) region had the highest rate of road traffic deaths in the world with an incidence of 26.6 road traffic deaths per 100,000 people per year compared to the global incidence of 18.2 road traffic deaths per 100,000 people per year (WHO Global Status Report on Road Safety, 2018). Overall, the large burden of TBIs in sub-Saharan Africa makes understanding TBI risk factors and outcomes an important global health concern.

In sub-Saharan Africa, patients presenting to hospitals with TBI suffer higher disability and mortality rates in comparison to TBI patients in HICs (De Silva et al., 2009; Georgoff et al., 2010; Eaton et al., 2017; Abdelgadir et al., 2017; Staton et al., 2017). This variation in TBI patient outcomes may be caused by differences in the availability of pre-hospital emergency services as well as the quality of in-hospital care (Sasser et al., 2006; De Silva et al., 2009; Kobusingye et al., 2010; Razzak et al., 2019). One important and well-established indicator of emergency care quality is time to treatment (McClelland et al., 2012; Cassalino et al., 2013; Sørup et al., 2013). Numerous studies in HICs have shown that pre- and in-hospital care delays commonly occur due to high patient volume and often result in worse outcomes (Wilper et al., 2008; Horwitz et al., 2010; Singer et al., 2011; Johnson et al., 2011; Carter et al., 2014; Morley et al., 2018; Berg et al., 2019; Groenland et al., 2019; McKenna et al., 2019). In LMICs, time metrics are also used to assess the quality of emergency department (ED) care (Aaronson et al., 2015; Broccoli et al., 2018). However, evidence of an association between ED care delays and patient outcomes in LMICs is limited and largely absent for locations in sub-Saharan Africa (London et al., 2001; Cavallaro et al., 2013; Yeboah et al., 2014; de Andrade et al., 2014; Béavogui et al., 2015; Khan et al., 2016). Consequently, there is a need to investigate the association between ED care delays and TBI patient outcomes in sub-Saharan Africa as a means of identifying areas of improvement in the delivery of patient care.

In addition to care delays, a lack of adequate medical infrastructure may contribute to poor TBI patient outcomes in sub-Saharan Africa. For example, limitations in equipment availability and timely treatment at a national referral hospital in Uganda

have been shown to increase TBI mortality from 7.8% to 62.0% (Kuo et al., 2017). Similarly, an inability to perform diagnostic procedures at a tertiary referral hospital in Tanzania was associated with an increased mortality of 47.0% among severe TBI patients (Staton et al., 2017). Reducing time to treatment and improving diagnostic capabilities within hospitals may therefore be one solution to improving TBI patient outcomes in low-resource settings. Such a solution may be achieved through the use of prognostic models.

Prognostic models have the potential to reduce time to treatment through optimization of patient triage and improvements in patient diagnosis. When applied to the field of healthcare, prognostic models support clinical decision making by using patient information to predict patient outcomes (Waljee et al., 2014; Giga et al., 2017; Nelson et al., 2019; Engelgau et al., 2019). In theory, a TBI specific prognostic model would allow healthcare professionals to quickly assess TBI patient prognosis upon hospital presentation thereby improving triage and resource allocation.

Most TBI prognostic models have been built using patient information from HICs (Pang et al., 2007; Kuo et al., 2011; Sobuwa et al., 2014; Silverberg et al., 2015; Junior et al., 2017). The most highly regarded TBI prognostic models to date were constructed using patient information from the International Mission on Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) database as well as the Corticosteroid Randomization After Significant Head Injury (CRASH) database (Steyerberg et al., 2008; MRC CRASH Trial Collaborators, 2008). While robust with regard to sample size, the IMPACT database consists largely of patients from HICs and

the CRASH database consist of patients from clinical trials (Roozenbeek et al., 2012). Consequently, prognostic models resulting from these databases may not be applicable to LMIC hospital settings.

In the most recent systematic review on prognostic models for mild, moderate, and severe TBI patients, only 5.0% of models incorporated data from LMICs (Perel et al., 2006). Additionally, no models included information regarding time to treatment (Perel et al., 2006). In a more recent systematic review of prognostic models for moderate TBI patients, no models incorporated data from LMICs or included information on time to treatment (Silverberg et al., 2015).

The WHO guidelines for essential trauma care stress the importance of reducing time to treatment for all trauma patients (WHO Guidelines for Essential Trauma Care, 2004). Moreover, delays to hospital admission, diagnostic procedures, and surgical treatment have been linked to higher mortality risks among TBI patients in sub-Saharan Africa (Vaca et al., 2019). Time to treatment information may therefore be useful in predicting outcomes for TBI patients. Overall, there is a need to develop TBI prognostic models for use in LMIC hospitals and which incorporate information regarding time to care.

To the best of my knowledge, few studies have analyzed the association between care delays and in-hospital outcomes among TBI patients in sub-Saharan Africa. Furthermore, no studies have developed time sensitive TBI prognostic models using patient data from sub-Saharan Africa. Accordingly, the objectives of this study were threefold: (1) describe the burden of care delays among a sample of TBI patients

presenting to a tertiary referral hospital in Tanzania, (2) assess associations between care delays and in-hospital outcomes among a sample of TBI patients presenting to a tertiary referral hospital in Tanzania, and (3) evaluate the efficacy of care delays as predictors of in-hospital outcomes in a prognostic model constructed with data from a sample of TBI patients presenting to a tertiary referral hospital in Tanzania.

2. Methods

2.1 Study Design and Participants

This study is a secondary analysis of a de-identified TBI patient registry collected from the Kilimanjaro Christian Medical Center (KCMC) ED in Moshi, Tanzania. Patients in the TBI registry were enrolled prospectively from May 2013 to August 2017. Inclusion into the registry was restricted to adult patients seeking care for acute TBI (<24 hours since time of injury) and who survived long enough to be evaluated by a physician in the ED. Patients who presented for follow-up were not eligible for inclusion into the registry (Staton et al., 2017). The registry data is non-longitudinal and contains information on demographics, mechanism of injury, vital signs, day of injury alcohol use, treatments received, time to treatment, and in-hospital outcomes. In total, 3209 patients were included in the registry.

2.2 Study Setting

Tanzania is an LMIC in East sub-Saharan Africa. In 2016, the age standardized rate of TBI in Tanzania was 332 cases per 100,000 people per year (GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, 2019). KCMC is a tertiary referral hospital in Moshi, Tanzania. It is the third largest hospital in the country and serves a population of over 15 million people. The KCMC ED receives around 1000 TBI patients annually, with about 300 requiring admission to the intensive care unit (ICU). In addition, the mortality rate of severe TBI patients presenting to KCMC ED is 47.0% (Staton et al., 2017).

2.3 Study Variables

Variables selected for inclusion into our analysis of care delays were age, sex, mechanism of injury, day of injury alcohol use, respiratory rate, systolic blood pressure, diastolic blood pressure, oxygen saturation, heart rate, Glasgow Coma Score (GCS), and time to care. Time to care variables included time from: (1) injury to hospital arrival, (2) hospital arrival to physician arrival, (3) physician arrival to receipt of lab tests, (4) physician arrival to receipt of an x-ray, (5) physician arrival to receipt of a brain computed tomography (CT) scan, (6) physician arrival to receipt of fluids, (7) physician arrival to receipt of oxygen, (8) physician arrival to receipt of a TBI surgery, (9) physician arrival to receipt of a non-TBI surgery (10), physician arrival to surgeon arrival (11), and physician arrival to ICU admission (12). The chronology of our time variables is

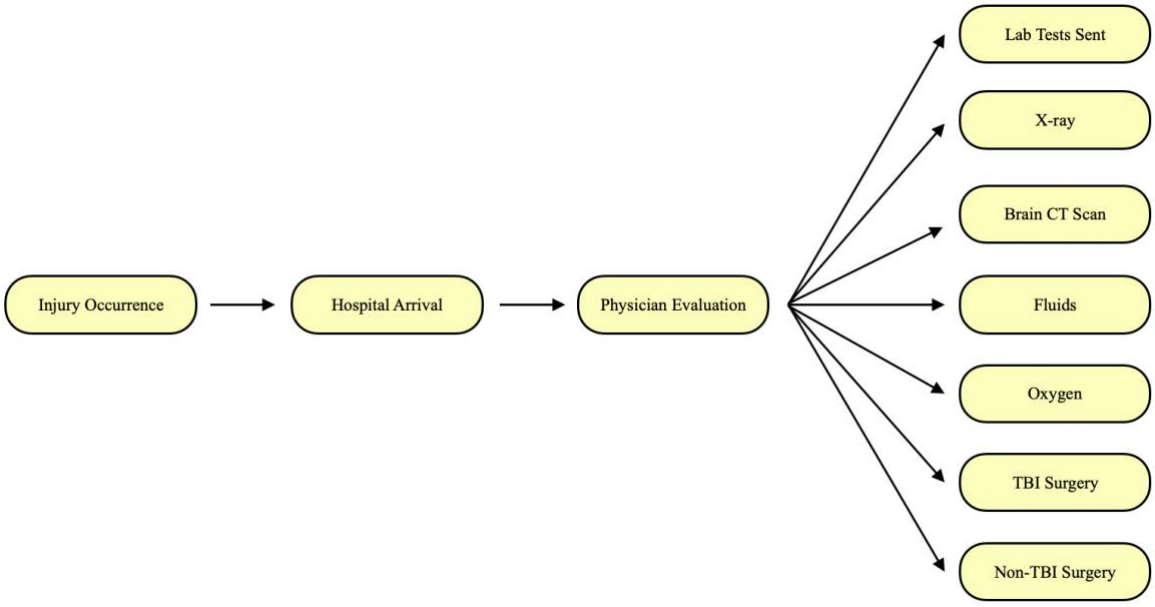

Figure 1: Chronological Sequence of Time to Treatment Variables

depicted in Figure 1. The outcome variable for our analysis of care delays was Glasgow Outcome Score (GOS) dichotomized as good (4-5) and poor (1-3). The Glasgow Outcome Scale is a validated measure used to assess recovery among trauma patients (McMillan et al., 2016). A patient's GOS is assigned at hospital discharge and ranges from one to five with the following categories: (1) death, (2) persistent vegetative state, (3) severe disability, (4) moderate disability, (5) good recovery. Good recovery is defined as a return to normal life with no more than minor cognitive deficits. Moderate disability is defined as having some reliance on special equipment, but requiring no assistance with daily living.

Variables used for prognostic model construction included all of the time to care variables listed above in addition to age, sex, mechanism of injury, intention of injury, day of injury alcohol use, temperature, respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation, pupil reactivity, GCS, ED disposition, receipt of TBI surgery, and receipt of non-TBI surgery. The outcome predicted by our prognostic models was GOS dichotomized as good (4-5) and poor (1-3). A summary of all variables in this study is provided in Table 1 below.

Table 1. Summary of Study Variables

Variable	Type	Unit if Numerical	Levels if Categorical	Included in Analysis of Care Delays	Included in Prognostic Models
Age	Numerical	Years	NA	✓	✓
Sex	Categorical	NA	Male, Female	✓	✓

Mechanism of Injury	Categorical	NA	Road Traffic Accident, Fall, Assault, Other	✓	✓
Day of Injury Alcohol Use	Categorical	NA	Yes, No	✓	✓
Intention of Injury	Categorical	NA	Self-Inflicted, Inflicted by Other, Unintentional, Unknown	X	✓
Respiratory Rate	Numerical	Breaths Per Minute	NA	✓	✓
Systolic Blood Pressure	Numerical	mmHg	NA	✓	✓
Diastolic Blood Pressure	Numerical	mmHg	NA	✓	✓
Oxygen Saturation	Numerical	Percent	NA	✓	✓
Heart Rate	Numerical	Beats Per Minute	NA	✓	✓
Right Pupil Reactivity	Categorical	NA	Reactive, Not Reactive, Unknown	X	✓
Left Pupil Reactivity	Categorical	NA	Reactive, Not Reactive, Unknown	X	✓
Pupils Equal	Categorical	NA	Yes, No, Unknown	X	✓
ED Disposition	Categorical	NA	ICU, Surgery, Operating Theatre, Home, Death	X	✓
TBI Surgery	Categorical	NA	Yes, No, Unknown	X	✓
Non-TBI Surgery	Categorical	NA	Yes, No, Unknown	X	✓

GCS	Categorical	NA	Mild, Moderate, Severe	✓	✓
Time to Hospital Arrival	Categorical	NA	0.0-1.0 h, 1.1-4.0 h, 4.1-12.0 h, >12.0 h	✓	✓
Time to Physician Arrival	Categorical	NA	0.0-15.0 m, 15.1-30.0 m, 30.1-45.0 m, >45.0 m	✓	✓
Time to Lab Tests	Categorical	NA	0.0-1.0 h, 1.1-4.0 h, 4.1-12.0 h, >12.0 h	✓	✓
Time to X-ray	Categorical	NA	0.0-1.0 h, 1.1-4.0 h, >4.0 h	✓	✓
Time to Brain CT	Categorical	NA	0.0-1.0 h, 1.1-4.0 h, >4.0 h, Not Received and Needed, Not Received and Not Needed	✓	✓
Time to Fluids	Categorical	NA	.0-1.0 h, 1.1-4.0 h, >4.0 h, Not Received and Needed, Not Received and Not Needed	✓	✓
Time to Oxygen	Categorical	NA	Received, Not Received and Needed, Not Received and Not Needed	✓	✓
Time to TBI Surgery	Categorical	NA	0.0-12.0 h, >12.0 h, Not Received	✓	✓
Time to non-TBI Surgery	Categorical	NA	0.0-12.0 h, >12.0 h, Not Received	✓	✓
Time to Surgeon Arrival	Categorical	NA	0.0-1.0 h, >1.0 h, Not Received	X	✓
Time to ICU Admission	Categorical	NA	0.0-1.0 h, 1.1-4.0 h, >4.0 h, Not Received	X	✓

2.4 Care Delay Analysis

Time Standards

The South African Triage Scale (SATS) is a triage protocol that was developed for use in LMICs by healthcare professionals of varying expertise (Gottschalk et al., 2006). Validity and reliability of the SATS have since been proven in a variety of rural and urban low-resource settings (Rosedale et al., 2011; Bruijns et al., 2008; Wangara et al., 2019; Dalwai et al., 2017; Dalwai et al., 2014; Rominski et al., 2014; Twomey et al., 2012). Using SATS time to treatment standards, we considered the following time intervals for our time to treatment variables: 0.0-1.0 hours, 1.1-4.0 hours, 4.1-12.0 hours, and greater than 12.0 hours.

Missing Data

Oxygen saturation and systolic blood pressure were used to identify patients in our dataset who experienced hypoxia (< 92% oxygen saturation) or hypotension (< 100 mmHg systolic). Using these binary indicators, we created two additional levels for our time to treatment variables: (1) patient did not receive the procedure and needed the procedure, and (2) patient did not receive the procedure and did not need the procedure. These levels were applied to our time to brain CT, time to fluids, and time to oxygen variables when observations were missing. Needing a brain CT scan was defined as having a GCS less than 13, needing fluids was defined as being hypotensive, and needing oxygen was defined as being hypoxic or having a GCS less than 8. The availability of time data for patients who received oxygen was insufficient for analysis,

so all such patients were classified as having received oxygen. For time to TBI surgery and time to non-TBI surgery, there was no way to identify a patient's need for surgery. As a result, patients with missing data for these variables were classified as having received or not received surgery.

After handling missing time to treatment data in the way described above, all variables in our data set with more than 20% of data missing were removed. One variable was removed during this process: (1) time to surgeon arrival. Time to ICU admission was also removed due to difficulties in calculating reliable time interval estimates for this variable. For all remaining variables, we used multivariate imputation by chained equations to impute missing values.

Descriptive Statistics

To describe differences in sociodemographic, injury, clinical, and time characteristics between our two outcome groups, we used t-tests and Fisher's exact tests. T-tests were used to identify differences in the mean of continuous variables between outcome groups. Similarly, Fisher's exact tests were used to identify differences in the distribution of observations within categorical variables between outcome groups. For each of these two tests, we report p-values.

Measures of Association

To quantify associations between sociodemographic, injury, clinical, and time characteristics with our outcome, we used logistic regression to model GOS as a function of our input variables. For all associations, we report crude and adjusted odds ratios and 95% confidence intervals (CIs). Associations were adjusted for age, sex, mechanism of

injury, respiratory rate, heart rate, oxygen saturation, systolic blood pressure, and GCS. In addition, we report adjusted estimates stratified by GCS. For all models, good outcome (GOS 4 to 5) was used as the outcome reference.

Software

All analyses were performed using R Language for Statistical Computing.

2.5 Prognostic Model Analysis

Data Pre-Processing

Categorization of time variables was handled in the same way described under section 2.4 and displayed in Table 1. Variables with more than 20% of observations missing were not included in model construction. During this step, we removed one variable: time to surgeon arrival. For the remaining variables we imputed missing values using ten iterations of predictive mean matching, logistic regression imputation, polytomous regression imputation, and proportional odds models. Following imputation, all variables were converted to indicator variables. After conversion to indicators, highly correlated variables (correlation coefficient ≥ 0.9 or ≤ -0.9) were dropped from our analysis to reduce redundancy in our predictive models. During this step, ten indicator variables were removed. In addition, we dropped any indicator variables with near zero variance because variables with little to no variance are poor predictors. No indicator variables were removed during this step. In total, our final dataset for model construction included 3180 patients and 50 indicator variables.

Internal Validation

All prediction models were trained and tested using five iterations of repeated ten-fold cross validation. During one iteration, our dataset is partitioned into ten subgroups and each of the ten subgroups serves as data on which to test the model that was trained using the remaining nine subgroups. The ten subgroups generated during data partitioning are uniquely different across iterations. We used the kappa statistic to select the optimal model from the pool of models generated from internal validation.

Resampling Strategy

With regard to our outcome of interest, the dataset used for this study is imbalanced as it is composed primarily of good outcome patients (85.8%) and very few poor outcome patients (14.2%). To improve our models' ability to predict poor outcomes for TBI patients, we used the synthetic minority oversampling technique (SMOTE) to resample minority observations (i.e. poor outcomes) during our internal validation procedure described above (Chawla et al., 2002).

Hyperparameter Optimization

Hyperparameters are parameters in prediction algorithms that are defined prior to training the prediction algorithm on a dataset. All other parameters in a prediction algorithm are derived during the training process. Consequently, optimal performance of a prediction algorithm is achieved when hyperparameters take on certain values. The average number of hyperparameters among the prediction algorithms used in this study was two. Optimization of hyperparameters in each of our prediction algorithms was achieved through a random search. In this process, random values were assigned to hyperparameters during each k-fold of our internal validation method.

Prediction Algorithms

K-Nearest Neighbors

In machine learning, pattern classification is the allocation of observations into defined classes. K-nearest neighbors is a classification algorithm whereby observations in a dataset are plotted in n-dimensional Euclidean space, where n is equal to the number of variables that define the observations in the dataset (Hu et al., 2016). Unclassified observations are then allocated to the same class as their nearest neighbor in Euclidean space, or to the class most represented by their k-nearest neighbors. To optimize performance of this classification algorithm, we let k range from 6 to 30 during internal validation.

Oblique Random Forests

Random forests are randomly generated decision trees used to allocate observations into classes. Typically, observations are plotted multiple times in two-dimensional space according to random pairs of variables. Partitions orthogonal to the axes of each plot are then generated to classify observations. Decisions trees can then be constructed from these partitions. However, orthogonal partitions may result in bias decision trees if observations have correlated features (Menze et al., 2011). To improve decision tree class discrimination, observations may be plotted in feature space with oblique partitions. Oblique partitions allow for the creation of more complex decision boundaries. Oblique random forests contain one hyperparameter, mtry, which defines the number of variables used to plot an observation. We let mtry assume random values during internal validation.

Bagged Classification and Regression Trees

Classification and regression trees are decision trees used to allocate observations into defined classes. Classification trees contain only categorical variables whereas regression trees may contain continuous variables. In a bagged classification and regression tree algorithm, a dataset is partitioned according to two variables on a cartesian plane (Loh et al., 2011). Ideally, such partitioning accurately separates observations by the class to which they belong. A decision tree can then be generated from the resulting partition. This process may be repeated with other variables and subsequent partitions may be added to the decision tree. We randomly paired all variables to generate partitions.

Bayesian Generalized Linear Regression

In Bayesian statistics, we model an outcome of interest as a probability distribution rather than a point estimate. In a Bayesian approach to linear regression, we begin by specifying a prior distribution representing the probability of our outcome. A prior distribution can be informed or uninformed by past studies. We then use our data to generate a likelihood function representing the probability of our outcome according to our dataset. Finally, we multiply the prior distribution by the likelihood function to obtain a posterior distribution representing the probability of our outcome based on both past and present information. For this study, we used the following uninformative prior distributions: normal distribution, t-distribution, and Cauchy distribution.

Single C5.0 Ruleset

The single C5.0 ruleset algorithm is a decision tree algorithm similar to random forests. However, the C5.0 algorithm is generally considered an improvement to random forests because it is computationally faster, uses less memory, reduces redundancy, and increases accuracy while generating smaller decision trees (Quinlan, 1993). The single C5.0 Ruleset algorithm used in this study does not contain hyperparameters.

Neural Network

Neural networks are prediction algorithms that mimic the human brain in a structural sense. In a neural network, input layer nodes represent the predictors in a dataset. Input nodes pass weighted values to output layer nodes. Multiple input nodes may converge on a single output node. In such a case, the output node sums the inputs via an activation function. Nodes located between the input and output layers are termed hidden layer nodes. Hidden nodes allow for complex and random interactions between predictors. Hidden nodes sum their inputs via an activation function and pass the resulting value to other hidden nodes or to output nodes (Zhang, 2016). For this study, we limited the number of hidden nodes to ten. In addition, we used a logistic sigmoid activation function for both the hidden and output layers. Input weights were randomly assigned and subsequently adjusted through internal validation iterations to minimize the sum of squared residuals.

Stochastic Gradient Boosting

Stochastic gradient boosting is a classification algorithm that uses decision trees to classify observations (Friedman, 1999). When we have a dichotomous classification scheme, stochastic gradient boosting begins by making an initial prediction for each

observation. The initial prediction is typically the average log odds of the reference outcome among all observations, and is thus the same for each observation. A pseudo residual is calculated for each observation by taking the difference between the observed and predicted value. A decision tree that predicts pseudo residuals is randomly generated. Predictions for each observation are updated by adding the initial prediction to the decision tree prediction scaled by a learning rate usually fixed at 0.1. Pseudo residuals are calculated for the updated predictions, and the process repeats until a set number of trees is generated.

Parallel Random Forest

The parallel random forest algorithm used in this study is a random forest algorithm as described above. However, this algorithm uses parallel processing to simultaneously generate multiple decision trees so as to optimize computer performance. The algorithm contains one hyperparameter, mtry, which defines the number of randomly selected predictors used to generate each tree. We let mtry assume random values during internal validation.

Model Comparisons

To ascertain the predictive value of our time to care variables, we tested each of the eight prediction algorithms above both with and without these variables. Models were compared using area under the receiver operating characteristic curve (AUC). Performance measures of our models without time to care variables have been previously published (Hernandes Rocha et al., 2019).

3. Results

3.1 Care Delay Analysis

Of the 3209 patients in our sample, 2848 (88.8%) had a good outcome and 361 (11.2%) had a poor outcome. Most patients were male (82.2%), sustained TBI through a road traffic incident (67.7%), and had a mild GCS (78.4%) (Table 2). The mean age of our sample was 32.1 years (SD 16.5). Most patients reached the hospital at least 1.0 hours after injury occurrence (81.1%), however 69.2% of patients were evaluated by a physician within 15.0 minutes of hospital arrival (Table 3). The most common wait time for receiving a lab test or an x-ray following physician evaluation was 0.0 to 1.0 hours (48.4% and 51.3% respectively). Most patients did not receive or need a brain CT scan (71.2%), but of those who did most waited more than 4.0 hours after physician evaluation to receive it (35.2%). Twenty-four percent of patients needed, but did not receive a brain CT scan. Most patients did not receive or need fluids (62.5%), but of those who did most waited 0.0 to 1.0 hours after physician evaluation to receive it (77.9%). Only 4.7% of patients needed, but did not receive fluids. Eighty-one percent of patients did not need or receive oxygen, 16.0% needed and did not receive oxygen, and 3.2% received oxygen. Most patients did not receive a TBI or non-TBI surgery (78.2% and 88.8% respectively). Of those who received surgery 56.6% and 54.2% waited more than 12.0 hours after physician evaluation to receive a TBI and non-TBI surgery respectively.

Table 2. Demographic and Clinical Characteristics of Sample and Their Crude Association with Poor Recovery

Variable	Total	Good Outcome	Poor Outcome	p-Value	Odds Ratio (95% CI)	p-Value
Age, Mean (SD)	32.1 (16.5)	31.5 (16.3)	36.3 (17.7)	<0.001	1.02 (1.01-1.02)	<0.001
Sex, N (%)				0.243		
Female	572 (17.8)	516 (18.1)	56 (15.5)		ref	
Male	2637 (82.2)	2332 (81.9)	305 (84.5)		1.21 (0.90-1.64)	0.224
Mechanism of Injury, N (%)				<0.001		
Assault	462 (14.4)	434 (15.2)	28 (7.8)		ref	
Road Traffic Injury	2171 (67.7)	1911 (67.1)	260 (72.0)		2.11 (1.43-3.22)	<0.001
Fall	347 (10.8)	293 (10.3)	54 (15.0)		2.86 (1.78-4.67)	<0.001
Other	229 (7.1)	210 (7.4)	19 (5.3)		1.40 (0.76-2.55)	0.274
Alcohol, N (%)				0.023		
No	2045 (63.7)	1835 (64.4)	210 (58.2)		ref	
Yes	1164 (36.3)	1013 (35.6)	151 (41.8)		1.30 (1.04-1.63)	0.020
Glasgow Coma Score, N (%)				<0.001		
Mild	2517 (78.4)	2438 (85.6)	79 (21.9)		ref	
Moderate	291 (9.1)	225 (7.9)	66 (18.3)		9.05 (6.34-12.90)	<0.001
Severe	401 (12.5)	185 (6.5)	216 (59.8)		36.03 (26.87-48.78)	<0.001
Respiratory Rate, Mean (SD)	21.9 (5.0)	21.7 (4.8)	23.0 (6.5)	0.020	1.04 (1.02-1.05)	<0.001
Systolic Blood Pressure, Mean (SD)	121.7 (21.6)	121.6 (20.5)	122.5 (28.6)	<0.001	1.00 (1.00-1.01)	0.478
Pulse Oxygen, Mean (SD)	95.4 (7.5)	96.2 (5.6)	88.8 (14.3)	0.006	0.92 (0.91-0.93)	<0.001
Heart Rate, Mean (SD)	88.0 (18.1)	87.5 (17.1)	91.9 (24.1)	<0.001	1.01 (1.01-1.02)	<0.001

Table 3. Time to Care Characteristics of Sample and Their Crude Association with Poor Recovery

Variable	Total	Good Outcome	Poor Outcome	p-Value	Odds Ratio (95% CI)	p-Value
Time to Arrival, N (%)				0.450		
0.0-1.0 h	607 (18.9)	536 (18.8)	71 (19.7)		ref	
1.1-4.0 h	1023 (31.9)	921 (32.3)	102 (28.3)		0.84 (0.61-1.16)	0.274
4.1-12.0 h	562 (17.5)	497 (17.5)	65 (18.0)		0.99 (0.69-1.41)	0.944
>12.0 h	1017 (31.7)	894 (31.4)	123 (34.1)		1.04 (0.76-1.42)	0.811

Time to Physician, N (%)				<0.001		
0.0-15.0 m	2220 (69.2)	1935 (67.9)	285 (78.9)		ref	
15.1-30.0 m	609 (19.0)	553 (19.4)	56 (15.5)		0.69 (0.50-0.92)	0.015
30.1-45.0 m	132 (4.1)	123 (4.3)	9 (2.5)		0.50 (0.23-0.93)	0.046
>45.0 m	248 (7.8)	237 (8.3)	11 (3.0)		0.32 (0.16-0.56)	<0.001
Time to Labs Sent, N (%)				<0.001		
0.0-1.0 h	1554 (48.4)	1340 (47.1)	214 (59.3)		ref	
1.1-4.0 h	1111 (34.6)	1010 (35.5)	101 (28.0)		0.63 (0.49-0.80)	<0.001
4.1-12.0 h	347 (10.8)	323 (11.3)	24 (6.6)		0.47 (0.29-0.71)	<0.001
>12.0 h	197 (6.1)	175 (6.1)	22 (6.1)		0.79 (0.48-1.23)	0.314
Time to X-ray, N (%)				<0.001		
0.0-1.0 h	1647 (51.3)	1427 (50.1)	220 (60.9)		ref	
1.1-4.0 h	1234 (38.5)	1123 (39.4)	111 (30.7)		0.64 (0.50-0.81)	<0.001
>4.0 h	328 (10.2)	298 (10.5)	30 (8.3)		0.65 (0.43-0.96)	0.037
Time to Brain CT, N (%)				<0.001		
0.0-1.0 h	39 (1.2)	31 (1.1)	8 (2.2)		ref	
1.1-4.0 h	55 (1.7)	45 (1.6)	10 (2.8)		0.86 (0.31-2.49)	0.777
>4.0 h	51 (1.6)	45 (1.6)	6 (1.7)		0.52 (0.16-1.63)	0.262
Not Received, Needed	778 (24.2)	503 (17.7)	275 (76.2)		2.12 (1.01-5.01)	0.063
Not Received, Not Needed	2286 (71.2)	2224 (78.1)	62 (17.2)		0.12 (0.05-0.26)	<0.001
Time to Fluids, N (%)				<0.001		
0.0-1.0 h	821 (25.6)	681 (23.9)	140 (38.8)		ref	
1.1-4.0 h	105 (3.3)	90 (3.2)	15 (4.2)		0.81 (0.44-1.40)	0.475
>4.0 h	128 (4.0)	112 (4.0)	16 (4.4)		0.69 (0.39-1.18)	0.198
Not Received, Needed	150 (4.7)	127 (4.5)	23 (6.4)		0.88 (0.53-1.40)	0.605
Not Received, Not Needed	2005 (62.5)	1838 (64.5)	167 (46.3)		0.44 (0.35-0.56)	<0.001
Time to Oxygen, N (%)				<0.001		
Received	104 (3.2)	33 (1.2)	71 (19.7)		ref	
Not Received, Needed	513 (16.0)	341 (12.0)	172 (47.6)		0.23 (0.15, 0.37)	<0.001
Not Received, Not Needed	2592 (80.8)	2474 (86.9)	118 (32.7)		0.02 (0.01, 0.03)	<0.001
Time to TBI Surgery, N (%)				0.002		
0.0-12.0 h	304 (9.5)	266 (9.3)	38 (10.5)		ref	
>12.0 h	397 (12.4)	332 (11.7)	65 (18.0)		1.37 (0.90-2.13)	0.152
Not Received	2508 (78.2)	2250 (79.0)	258 (71.5)		0.80 (0.56-1.17)	0.234

Time to Non-TBI Surgery, N (%)				0.414		
0.0-12.0 h	164 (5.1)	146 (5.1)	18 (5.0)		ref	
>12.0 h	194 (6.0)	178 (6.3)	16 (4.4)		0.73 (0.36-1.48)	0.382
Not Received	2851 (88.8)	2524 (88.6)	327 (90.6)		1.05 (0.65-1.80)	0.847

Four hundred and one (12.5%) patients presented with a severe TBI. Among these critically injured patients, the mean age was 32.6 years (SD 17.9) and most were male (85.5%) and sustained injury through a road traffic incident (71.8%). A majority of severe patients reached the hospital at least 1.0 hours after injury occurrence (80.1%), but nearly all (81.8%) waited no more than 15.0 minutes to be evaluated by a physician upon

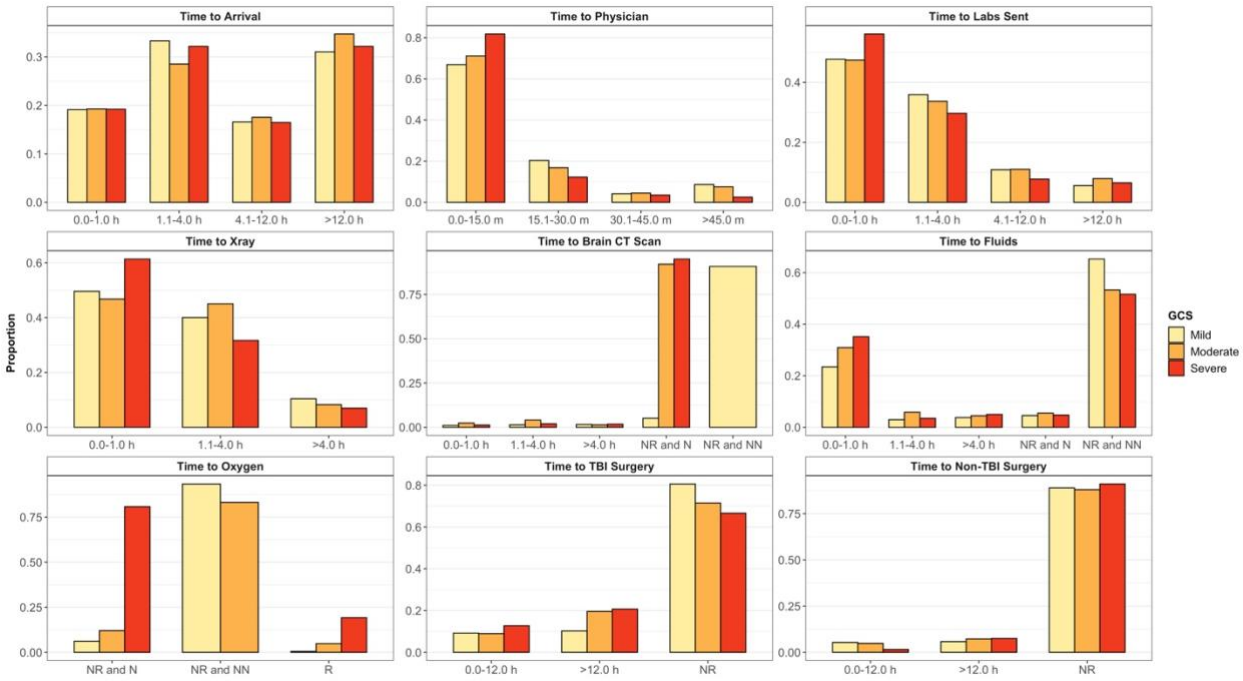

Figure 2. Proportion of Mild, Moderate, and Severe TBI Patients in each Category of Time to Care Variables. R = Received, NR = Not Received, N = Needed, NN = Not Needed.

arrival (Figure 2). Following physician evaluation, a majority of severe patients waited 0.0 to 1.0 hours to receive lab tests (56.1%) or an x-ray (61.3%). Unfortunately, 95.0% of severe cases needed but did not receive a brain CT scan while 80.8% needed but did not

receive oxygen. Most severely injured patients did not need fluids (51.6%). Of those who received fluids, most waited no more than 1.0 hours after physician evaluation to receive it (80.6%). A majority of severe cases did not receive TBI or non-TBI surgery (66.6% and 91.0% respectively). However, of those who received a TBI or non-TBI surgery most waited more than 12.0 hours after physician evaluation for the procedure (60.4% and 83.3% respectively).

In our unadjusted models, a higher age, respiratory rate, systolic blood pressure, and heart rate were associated with higher odds of a poor outcome (Table 2). High oxygen saturation lowered the odds of a poor outcome. In comparison to patients who sustained TBI through assault, those who suffered a TBI by road traffic incidents or falls had higher odds of a poor outcome. Patients who self-reported day of injury alcohol use had higher odds of a poor outcome compared to those who did not report day of injury alcohol use. In comparison to mild cases, moderate and severe cases had higher odds of a poor outcome. Finally, patients with higher respiratory rates, higher heart rates, or lower oxygen saturation had higher odds of a poor outcome.

In our unadjusted models of care delays, waiting more than 15.0 minutes to see a physician upon hospital arrival was associated with reduced odds of a poor outcome in comparison to waiting 15.0 minutes or less (Table 3). Similarly, in comparison to patients who waited 0.0 to 1.0 hours to receive a lab test or x-ray, those who waited longer had lower odds of a poor outcome. Patients who did not receive nor need a brain CT scan or fluids had lower odds of a poor outcome in comparison to those who received these procedures within 1.0 hours or less of physician evaluation. Compared to patients who

received oxygen, those who did not receive and needed oxygen as well as those who did not receive nor need oxygen had lower odds of a poor outcome.

In our adjusted models of care delays, patients who waited 1.1 to 4.0 hours after physician evaluation to receive lab tests had lower odds of a poor outcome (OR: 0.61; 95% CI: 0.43, 0.86) compared to those who waited 0.0 to 1.0 hours (Figure 3). In

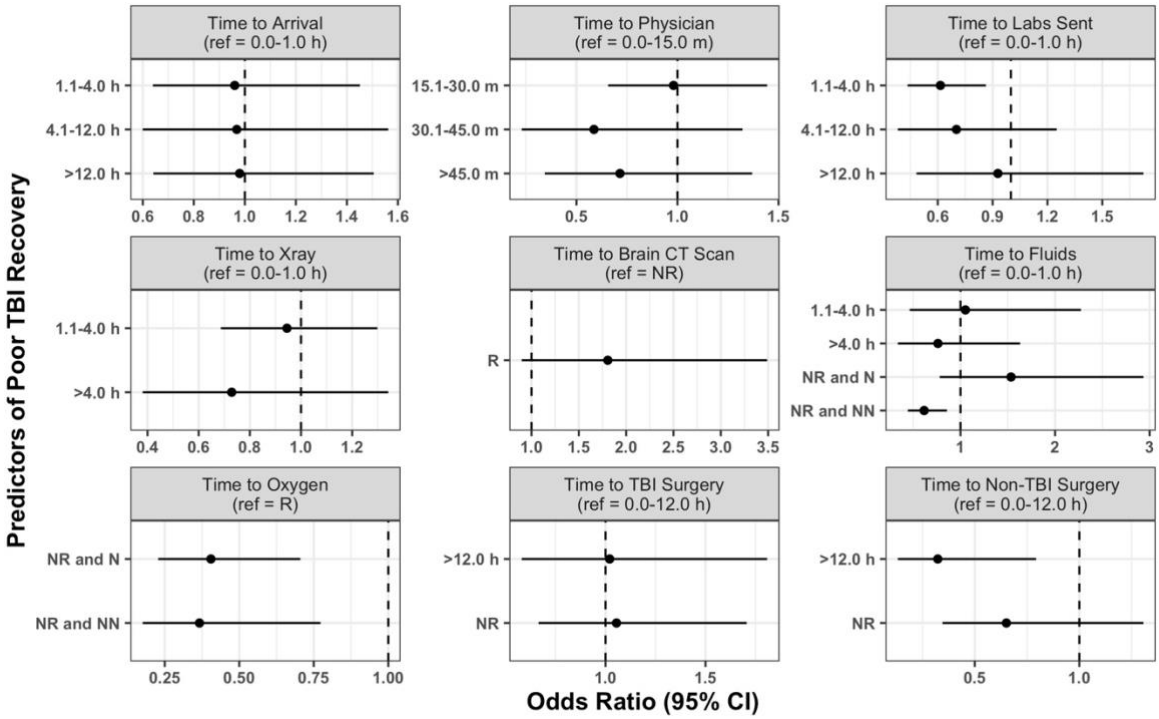

Figure 3. Adjusted Logistic Regression of Time to Care Variables. R = Received, NR = Not Received, N = Needed, NN = Not Needed.

comparison to patients who received fluids within 1.0 hours of physician evaluation, those who did not need fluids had lower odds of a poor outcome (OR: 0.62; 95% CI: 0.44; 0.86). Patients who needed and did not receive oxygen (OR: 0.40; 95% CI: 0.22, 0.70) as well as those who did not need and did not receive oxygen (OR: 0.37; 95% CI: 0.18, 0.77) had lower odds of a poor outcome compared to patients who received oxygen. Finally, patients who received a non-TBI surgery more than 12.0 hours after physician

evaluation had lower odds of a poor outcome (OR: 0.32; 95% CI: 0.13, 0.79) compared to those who received a non-TBI surgery within 12.0 hours.

Stratification of our adjusted care delay models revealed effect measure modification by GCS on the multiplicative scale (Figure 4). For our variable time to labs

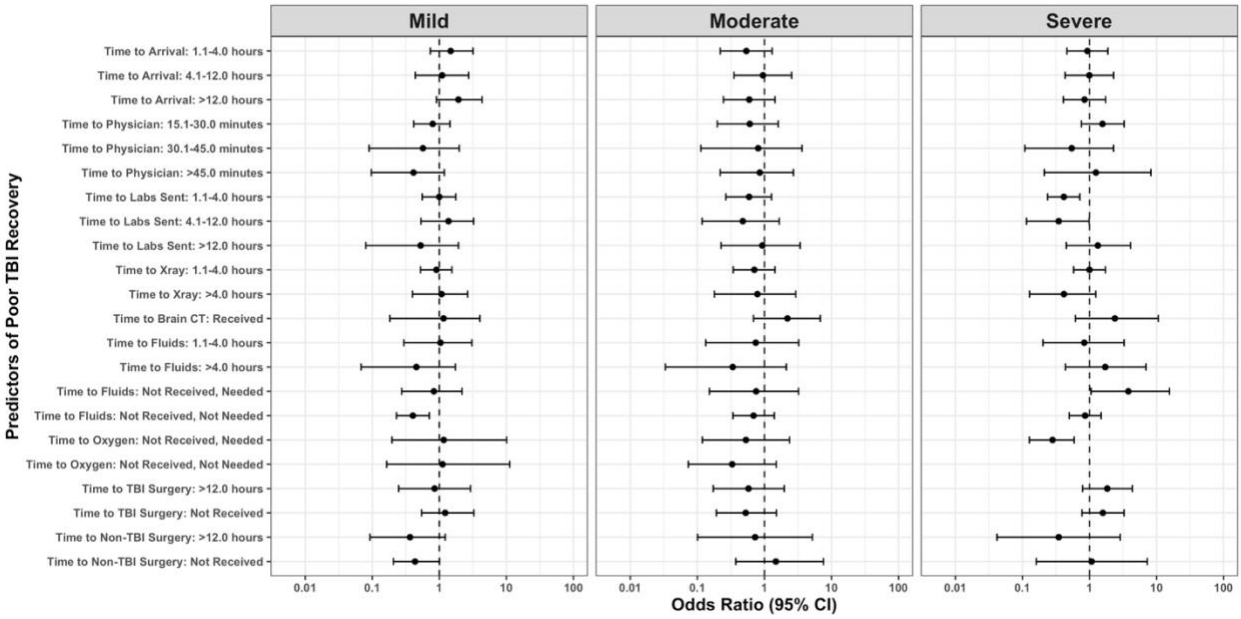

Figure 4. Adjusted Logistic Regression of Time to Care Variables Stratified by GCS.

sent, non-null associations were observed only among severe cases. Severe patients who waited 1.1 to 4.0 hours (OR: 0.41; 95% CI: 0.24, 0.72) or 4.1 to 12.0 hours (OR: 0.35; 95% CI: 0.11, 0.98) after physician evaluation to receive lab tests had lower odds of a poor outcome. For our variable time to fluids, non-null associations only occurred among mild cases. Mild patients who did not need and did not receive fluids had lower odds of a poor outcome (OR: 0.40; 95% CI: 0.23, 0.71). For our variable time to oxygen, non-null associations occurred only among severe cases. Severe patients who needed and did not receive oxygen had lower odds of a poor outcome (OR: 0.28; 95% CI: 0.13, 0.59). For our

variable time to non-TBI surgery, non-null associations only occurred among mild cases. Mild patients who waited more than 12.0 hours after physician evaluation to receive a non-TBI surgery (OR: 0.36; 95% CI: 0.09, 1.22) as well as those who did not receive a non-TBI surgery (OR: 0.43; 95% CI: 0.21, 1.01) had lower odds of a poor outcome.

3.2 Prognostic Model Analysis

Of the 3140 patients included in our prognostic model, 2695 (85.8%) had a good outcome and 445 (14.2%) had a poor outcome. The mean age of our patient sample was 31.2 years (SD 15.2). A majority of patients were male (82.3%) and sustained TBI through a road traffic incident (82.6%). Twenty-five percent of patients self-reported day of injury alcohol use. The mean GCS was 13.3 (SD 3.2) for the total sample, 13.9 (SD 2.4) for the good outcome group, and 8.1 (SD 4.3) for the poor outcome group. Respiratory rate, heart rate, oxygen saturation, and pupil reactivity differed significantly by outcome status (Table 4). In total, 671 (21.4%) patients received a TBI surgery and 379 (12.1%) received a non-TBI surgery.

Table 4. Demographic and Clinical Characteristics of Prognostic Model Sample

Variable	Total	Good Outcome	Poor Outcome	p-Value
Age, Mean (SD)	31.2 (15.3)	30.8 (15.2)	34.2 (15.4)	<0.001
Sex, N (%)				0.352
Male	2583 (82.3)	2285 (82.0)	298 (84.2)	
Female	557 (17.7)	501 (18.0)	56 (15.8)	
Mechanism of Injury, N (%)				<0.001
Car RTI	588 (18.7)	505 (18.1)	83 (23.4)	
Motorcycle RTI	1574 (50.1)	1397 (50.1)	177 (50.0)	

Pedestrian RTI	432 (13.8)	369 (13.2)	63 (17.8)	
Assault	118 (3.8)	111 (4.0)	7 (2.0)	
Gun	17 (0.5)	14 (0.5)	3 (0.8)	
Knife	150 (4.8)	143 (5.1)	7 (2.0)	
Domestic Violence	261 (8.3)	247 (8.9)	14 (4.0)	
Intention of Injury, N (%)				<0.001
Self-Inflicted	2 (0.0)	1 (0.0)	1 (0.3)	
Inflicted by Other	533 (17.0)	500 (17.9)	33 (9.3)	
Unintentional	2585 (82.3)	2272 (81.6)	313 (88.4)	
Unknown	20 (0.6)	13 (0.5)	7 (2.0)	
Day of Injury Alcohol Use, N (%)				<0.001
Yes	799 (25.4)	715 (25.7)	84 (23.7)	
No	1533 (48.8)	1399 (50.2)	134 (37.9)	
Unknown	808 (25.7)	672 (24.1)	136 (38.4)	
Temperature, Mean (SD)	36.5 (0.7)	36.4 (0.7)	36.5 (1.1)	0.090
Respiratory Rate, Mean (SD)	21.8 (3.9)	21.6 (3.7)	22.8 (5.2)	<0.001
Heart Rate, Mean (SD)	88.0 (18.2)	87.6 (17.4)	91.3 (23.6)	0.004
Systolic Blood Pressure, Mean (SD)	121.7 (20.2)	121.9 (19.4)	120.5 (25.5)	0.333
Diastolic Blood Pressure, Mean (SD)	72.6 (14.8)	72.8 (14.4)	71.2 (17.6)	0.092
Pulse Oxygen, Mean (SD)	95.5 (7.2)	96.4 (5.2)	89.1 (14.1)	<0.001
GCS, Mean (SD)	13.3 (3.2)	13.9 (2.4)	8.1 (4.3)	<0.001
Right Pupil, N (%)				<0.001
Reactive	2992 (95.3)	2747 (98.6)	245 (69.2)	
Not Reactive	135 (4.3)	29 (1.0)	106 (29.9)	
Unknown	13 (0.4)	10 (0.4)	3 (0.8)	
Left Pupil, N (%)				<0.001
Reactive	3017 (96.1)	2752 (98.8)	265 (74.9)	
Not Reactive	109 (3.5)	23 (0.8)	86 (24.3)	
Unknown	14 (0.4)	11 (0.4)	3 (0.8)	
Pupils Equal, N (%)				<0.001
Yes	908 (28.9)	824 (29.6)	84 (23.7)	
No	20 (0.6)	8 (0.3)	12 (3.4)	
Unknown	2212 (70.4)	1954 (70.1)	258 (72.9)	
				<0.001

ED Disposition, N (%)				
ICU	86 (2.7)	34 (1.2)	52 (14.7)	
Surgery	2674 (85.2)	239 (86.1)	276 (78.0)	
Operating Theatre	14 (0.4)	13 (0.5)	1 (0.3)	
Home	340 (10.8)	340 (12.2)	0 (0.0)	
Death	26 (0.8)	0 (0.0)	26 (7.1)	
TBI Surgery, N (%)				<0.001
Yes	671 (21.4)	569 (20.4)	102 (28.8)	
No	2268 (72.2)	2017 (72.4)	251 (70.9)	
Unknown	201 (6.4)	200 (7.2)	1 (0.3)	
Other Surgery, N (%)				<0.001
Yes	379 (12.1)	336 (12.1)	43 (12.1)	
No	2554 (81.3)	2245 (80.6)	309 (87.3)	
Unknown	207 (6.6)	205 (7.4)	2 (0.6)	

Time to care characteristics of our prognostic model patient sample are described in Table 5. Most patients reached the hospital more than 12.0 hours after injury occurrence (31.8%). However, most patients were seen by a physician within 1.0 hours of hospital arrival (94.8%). Following physician evaluation, the most common wait time to receive lab tests was 0.0 to 1.0 hours (48.6%). Similarly, the most common wait time to receive a skull or chest x-ray was 0.0 to 1.0 hours (48.8% and 49.2% respectively). Most patients did not need nor receive a brain CT scan (71.9%), fluids (62.3%), or oxygen (90.0%). In addition, most patients did not receive a TBI or non-TBI surgery (82.4% and 90.8% respectively). Lastly, 91.4% of patients were not admitted to the ICU. However, of those who were admitted to the ICU, most waited more than 4.0 hours after physician evaluation to be admitted (76.8%).

Table 5. Time to Care Characteristics of Prognostic Model Sample

Variable	Total	Good Outcome	Poor Outcome	p-Value
Time to Arrival, N (%)				0.791
0.0-1.0 h	592 (18.9)	522 (18.7)	70 (19.8)	
1.1-4.0 h	975 (31.1)	869 (31.2)	106 (29.9)	
4.1-12.0 h	575 (18.3)	515 (18.5)	60 (16.9)	

>12.0 h	998 (31.8)	880 (31.6)	118 (33.3)	
Time to Physician, N (%)				0.046
0.0-1.0 h	2976 (94.8)	2633 (94.5)	343 (96.9)	
1.1-4.0 h	118 (3.8)	113 (4.1)	5 (1.4)	
>4.0 h	46 (1.5)	40 (1.4)	6 (1.7)	
Time to Labs Sent, N (%)				<0.001
0.0-1.0 h	1526 (48.6)	1311 (47.1)	215 (60.7)	
1.1-4.0 h	1069 (34.0)	975 (35.0)	94 (26.6)	
4.1-12.0 h	342 (10.9)	318 (11.4)	24 (6.8)	
>12.0 h	203 (6.5)	182 (6.5)	21 (5.9)	
Time to Chest X-ray, N (%)				0.027
0.0-1.0 h	1531 (48.8)	1349 (48.4)	182 (51.4)	
1.1-4.0 h	1047 (33.3)	950 (34.1)	97 (27.4)	
>4.0 h	562 (17.9)	487 (17.5)	75 (21.2)	
Time to Skull X-ray, N (%)				0.008
0.0-1.0 h	1546 (49.2)	1353 (48.6)	193 (54.5)	
1.1-4.0 h	1210 (38.5)	1100 (39.5)	110 (31.1)	
>4.0 h	384 (12.2)	333 (12.0)	51 (14.4)	
Time to Brain CT Scan, N (%)				<0.001
0.0-1.0 h	37 (1.2)	29 (1.0)	8 (2.3)	
1.1-4.0 h	54 (1.7)	45 (1.6)	9 (2.5)	
>4.0 h	50 (1.6)	45 (1.6)	5 (1.4)	
Not Received, Needed	741 (23.6)	489 (17.6)	252 (71.2)	
Not Received, Not Needed	2258 (71.9)	2178 (78.2)	80 (22.6)	
Time to Fluids, N (%)				<0.001
0.0-1.0 h	812 (25.9)	672 (24.1)	140 (39.5)	
1.1-4.0 h	102 (3.2)	88 (3.2)	14 (4.0)	
>4.0 h	126 (4.0)	111 (4.0)	15 (4.2)	
Not Received, Needed	144 (4.6)	118 (4.2)	26 (7.3)	
Not Received, Not Needed	1956 (62.3)	1797 (64.5)	159 (44.9)	
Time to Oxygen, N (%)				<0.001
0.0-1.0 h	77 (2.5)	25 (0.9)	52 (14.7)	
>1.0 h	20 (0.6)	5 (0.2)	15 (4.2)	
Not Received, Needed	219 (7.0)	126 (4.5)	93 (26.3)	
Not Received, Not Needed	2824 (90.0)	2630 (94.4)	194 (54.8)	
Time to TBI Surgery, N (%)				0.027
0.0-4.0 h	77 (2.5)	71 (2.5)	6 (1.7)	
4.1-12.0 h	165 (5.3)	142 (5.1)	23 (6.5)	
>12.0 h	312 (9.9)	263 (9.4)	49 (13.8)	
Not Received	2586 (82.4)	2310 (82.9)	276 (78.0)	
Time to non-TBI Surgery, N (%)				0.186
0.0-4.0 h	51 (1.6)	42 (1.5)	9 (2.5)	
4.1-12.0 h	83 (2.6)	76 (2.7)	7 (2.0)	
>12.0 h	156 (5.0)	144 (5.2)	12 (3.4)	
Not Received	2850 (90.8)	2524 (90.6)	326 (92.1)	
Time to ICU Admission, N (%)				<0.001
0.0-1.0 h	14 (0.4)	5 (0.2)	9 (2.5)	
1.1-4.0 h	50 (1.6)	19 (0.7)	31 (8.8)	
>4.0 h	212 (6.8)	146 (5.2)	66 (18.6)	
Not Received	2864 (91.2)	2616 (93.9)	248 (70.1)	

We tested eight different prediction algorithms on our patient sample. The AUC of each of our eight models with and without our time to care variables are presented in Table 6. The k-nearest neighbor algorithm produced a time sensitive model with the lowest AUC (71.3; 95% CI: 71.1, 71.5). The Bayesian generalized linear regression algorithm produced a time sensitive model with the highest AUC (89.5; 95% CI: 88.8, 90.3) making it the most useful in predicting in-hospital outcomes among TBI patients presenting to KCMC. The time sensitive Bayesian model had an accuracy of 0.87, a sensitivity of 0.89, a specificity of 0.74, and a kappa statistic of 0.55.

Table 6. AUC and 95% CI of Prediction Models with and without Time to Care Variables

Prediction Algorithm	AUC (95% CI) - Without Time to Care Variables (Hernandes Rocha et al., 2019)	AUC (95% CI) - With Time to Care Variables
K Nearest Neighbors	66.2 (66.1, 65.5)	71.3 (71.1, 71.5)
Oblique Random Forests	84.8 (84.5, 85.3)	88.5 (88.3, 88.8)
Bagged Classification and Regression Trees	83.6 (82.7, 84.6)	85.6 (84.7, 86.5)
Bayesian Generalized Linear Regression	86.5 (85.6, 87.4)	89.5 (88.8, 90.3)
Single C5.0 Ruleset	79.8 (78.8, 80.9)	80.6 (79.6, 81.6)
Stochastic Gradient Boosting	85.1 (84.9, 85.3)	87.8 (87.7, 88.0)
Neural Network	78.8 (77.8, 80.0)	83.7 (82.8, 84.7)
Parallel Random Forest	84.9 (84.6, 85.3)	88.0 (87.2, 88.9)

As shown in Table 6, the inclusion of time to care variables in our sample increased the AUC of each of our models. More importantly, our time to care variables were strong predictors of in-hospital outcome in each of our top three performing

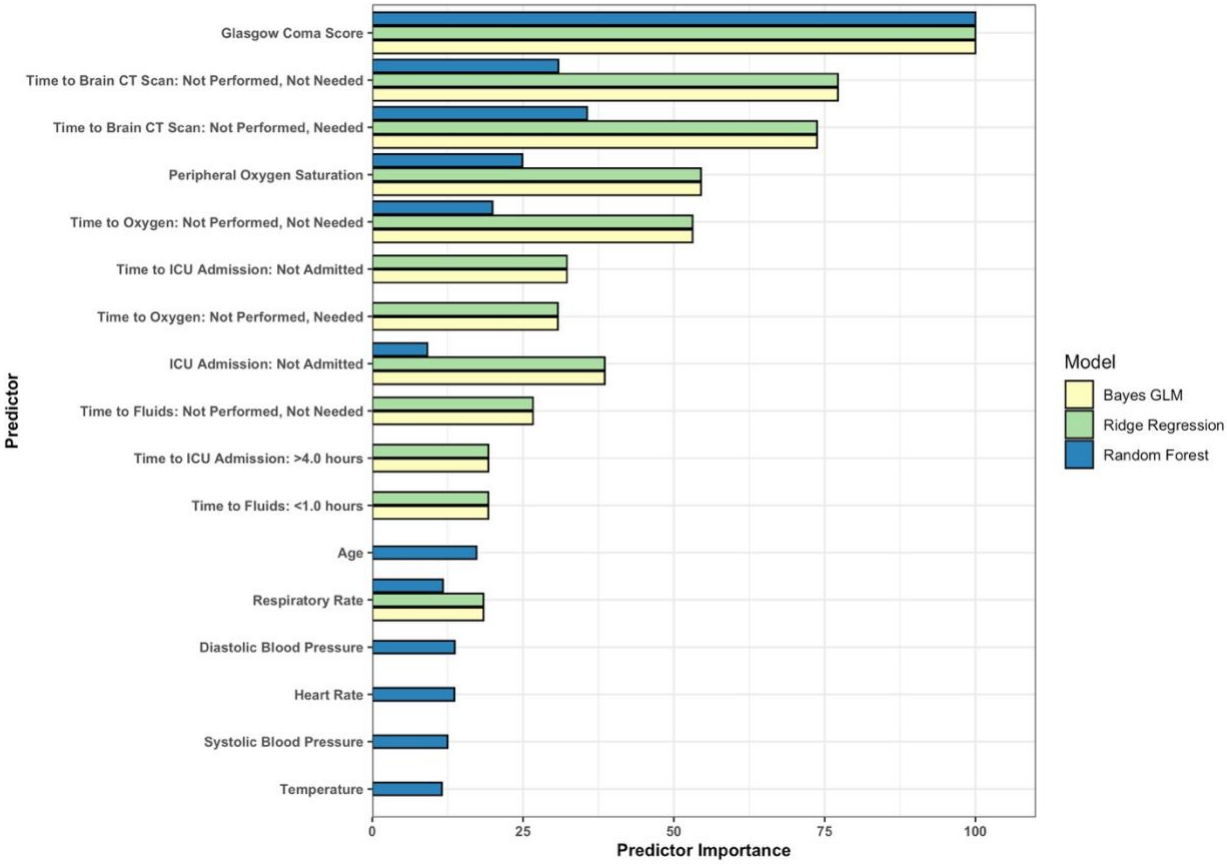

Figure 5. Top Predictors of a Poor Outcome in Three Best Performing Models.

models (Figure 5). In our Bayesian and oblique random forest models (top two models), nine of the eleven top predictors of a poor outcome were time to care variables. In our parallel random forest model (top third model), four of the top six predictors of a poor outcome were time to care variables. The top predictor of a poor outcome in all models was GCS.

4. Discussion

4.1 Care Delay Analysis

To our knowledge, this analysis is the first to examine the relationship between care delays and in-hospital outcomes among TBI patients in Tanzania. Our results convey three primary findings regarding care delays among our TBI patient sample. First, delays to physician evaluation following hospital arrival are infrequent. Second, patient access to diagnostic and treatment procedures is inadequate. Third, in-hospital outcomes are more commonly associated with need for care rather than time to care.

An absence of delays to physician evaluation following hospital arrival suggests patients are evaluated promptly and triaged appropriately. Table 1 shows that 69.2% of all TBI patients were evaluated by a physician within 15.0 minutes of hospital arrival, 88.2% within 30.0 minutes, and 95.0% within 45.0 minutes. According to the SATS, the ideal time to physician evaluation upon hospital arrival for emergency, very urgent, and urgent trauma cases is immediately, less than 10 minutes, and less than 1.0 hours respectively (SATS Manual., 2012). The evaluation of nearly all TBI patients within the time recommended by SATS for urgent cases demonstrates timely evaluation. In addition, 81.8% of patients evaluated within 15.0 minutes of hospital arrival were severely injured. Evaluation of severe patients within the time recommended by SATS for emergency and very urgent cases suggests efficient triage prioritizing the critically injured. Moreover, our data is consistent with wait times in HIC EDs. A comprehensive evaluation of 364 EDs in the United States revealed an average evaluation wait time of 52.4 minutes for all patients and 31.8 minutes for emergency cases (Horwitz et al., 2010).

Evaluation wait times among our patient sample are therefore accordant with standards applied in both LMICs (by SATS) and HICs.

Inadequate access to radiological imaging among our patient sample highlights an element of TBI patient care requiring substantial improvement. Over 92.0% of moderately injured patients and 95.0% of severely injured patients needed, but did not receive a brain CT scan (Figure 2). Limited access to medical imaging appears to be a problem afflicting all regions of Tanzania. In 2014, a comprehensive evaluation of registered radiological equipment estimated 5.7 general radiography units per one million people in Tanzania; significantly lower than the WHO recommended 20.0 units per one million people (Ngoya et al., 2016). In addition, medical imaging resources appeared to be evenly distributed across geographic regions suggesting limited access or delayed access to radiological equipment occurs across the country. Access to medical imaging observed among our sample and the whole of Tanzania is consistent with data from Uganda, a neighboring sub-Saharan LMIC. In 2012, only 56.0% of patients in urban areas of Uganda and 13.0% of patients in rural areas who required medical imaging received an imaging procedure (Kawooya, 2012). Given the shortage of imaging procedures provided in Tanzania and Uganda, efforts should be made to further quantify the need for medical imaging equipment in this region of the world as well as its impact on patient outcomes.

In comparison to care delays, a patient's need for care and whether or not care was received appear to be stronger predictors of in-hospital outcome. In our adjusted regression models, significant associations were more prevalent among variables

indicating need and receipt rather than variables indicating delays (Figure 3). Consequently, binary variables indicating care need and care receipt status may be more useful than time to care data in assessing patient prognosis. Under emergency department conditions characterized by overcrowding, as is common in both HICs and LMICs, the collection of accurate time to care data as a patient progresses through their hospital stay may be difficult and of little use to physicians. Using care need and care receipt status to inform patient prognosis may therefore be both a more useful and practical option.

4.2 Study Limitations

Interpretation of our results is not complete without careful consideration of limitations. First, the TBI registry used in this study likely underrepresents the most severe TBI patients. Severely injured patients are more likely to die before reaching the hospital and are therefore less likely to appear in a hospital registry. While care delays may have the greatest impact on severe TBI patients, our registry only captured patients well enough to reach the hospital.

Second, our variable time to hospital arrival was based on self-reported or family-reported information regarding the time of injury occurrence. Such information bias may have led to exposure misclassification within our time to hospital arrival variable. However, all time information was recorded in the patient registry before ascertainment of patient outcomes. Thus, any exposure misclassification would have been independent of patient outcome status. Such non-differential exposure misclassification would bias our measure of association towards the null.

Third, our analysis only included patients presenting to KCMC. Given KCMC is a national referral hospital, patient outcomes at this medical center may be better in comparison to less resourced hospitals in surrounding regions. Care delays may have a stronger impact on patients with access to a lower quality of care. Consequently, associations between care delays and patient outcomes presented in this study may be stronger in areas outside of the Kilimanjaro region of Tanzania.

4.3 Prognostic Model Analysis

To our knowledge, this is the first analysis to incorporate machine learning and time to care data into construction of a TBI prognostic model for use in an LMIC. Our results convey three primary findings regarding TBI prognostic models in low-resource settings. First, machine learning can generate prognostic models that are sufficiently accurate to inform clinical decision making in LMICs. Second, time to care data can be highly valuable to patient prognosis. Third, machine learning prognostic models can be both useful and interpretable.

The application of machine learning to patient prognosis in an LMIC represents significant progress towards integrating artificial intelligence and clinical decision making in low-resource settings. To date, the application of prognostic models to TBI patients has been almost entirely restricted to HICs (Perel et al., 2006; Silverberg et al., 2015). Our use of a 3140 patient registry from Tanzania to build a TBI prognostic model is a notable step towards representing LMICs in the rapidly advancing field of clinical decision support systems. Furthermore, within the field of neurosurgical care, machine learning has become the predominant method used to assemble prediction models due

to its ability to outperform both classical statistical models and clinicians (Senders et al., 2018; Senders et al., 2018). We obtained a prognostic model with an AUC of 89.5 and accuracy of 0.87 indicating the successful application of a machine learning algorithm to LMIC data. Such an achievement demonstrates the potential of using a machine learning based TBI prognostic model to support clinicians in low-resource hospitals.

The incorporation of time to care data into our TBI prognostic models represents the enormous potential of such data in patient prognosis. The inclusion of time to care variables improved the AUC and accuracy of each of our eight models, allowing us to achieve a top AUC of 89.5 (95% CI: 88.8, 90.3) and a top accuracy of 0.87. For comparison, TBI prognostic models constructed from the CRASH and IMPACT databases achieved AUCs of 88.0 and 84.0 respectively (Steyerberg et al., 2008; MRC CRASH Trial Collaborators, 2008). More importantly, our time to care variables comprised a majority of the top predictors of a poor outcome in our top three performing models (Figure 5) indicating the predictive value of care delays. In theory, a TBI prognostic model in a low-resource setting would be used to assess patient prognosis upon hospital presentation to support clinician judgement. However, diagnostic and treatment delays experienced by a patient as they progress through their hospital stay could be used to continuously update prognosis. The result would be a prognostic model that supports clinicians during every step of patient care.

Although the usefulness of a TBI prognostic model has been demonstrated, the practicality of such a tool depends largely on clinician acceptance. In a survey of 60 doctors from both LMICs and HICs who routinely treat head injuries, 63.0% did not

agree they assess patient prognosis accurately and 67.0% stated an accurate prognostic model would influence how they manage patients (Perel et al., 2007). While a single survey does not represent the views of physicians globally, it is evidence of receptiveness towards prognostic models within the global medical community. In an additional survey, doctors from an HIC perceived prognostic models as valuable confirmatory tools that both augment decision making and facilitate patient communication (Hallen et al., 2015). However, trust in a prognostic model stems largely from understanding its underlying mechanisms. Machine learning algorithms underlying prognostic model outputs, although accurate, can be unpredictable and difficult to interpret. Our Bayesian generalized linear model uses transparent statistics and provides easily interpretable outputs, thus demonstrating the ability to create accurate and user-friendly machine learning based clinical decision support tools.

4.4 Implications for Further Research

Moving forward, we plan to improve our prognostic model in two ways. First, we would like to incorporate additional TBI patient registries into our training dataset. Currently, our training dataset contains only patients from KCMC in Tanzania. To expand our model's usefulness such that it is applicable to a larger array of clinical circumstances experienced by patients in low-resource settings, data from other regions of Tanzania as well as other LMICs is required.

Second, we would like to externally validate our prognostic model. A large proportion of published TBI prognostic models are never validated on external populations (Perel et al., 2006). External validations are an indication of a prognostic

model's clinical effectiveness (Senders et al., 2018). To demonstrate clinical validity and reliability of our model, we hope to validate it on populations outside of Tanzania's Kilimanjaro region.

Lastly, we would like to perform a feasibility study of our prognostic model to gauge its acceptance among clinicians. Ideally, we would create a user-friendly interface for the model and introduce it to healthcare professionals involved in the care pathway of TBI patients at KCMC. Feedback could then be incorporated into our model to increase its usefulness to physicians.

4.5 Study Strengths and Limitations

Our greatest strength in constructing a TBI prognostic model was access to a robust TBI patient registry. Again, in a systematic review of TBI prognostic models, most models assessed used less than 500 patients (Perel et al., 2006). Our registry of 3180 TBI patients provided ample data on which to train a TBI specific prognostic model. Moreover, such a large sample size has yet to be used in TBI prediction models in sub-Saharan Africa. However, there are limitations to our model which must be considered.

First, several of our time to care variables had large amounts of missing data. To compensate, we created variable categories indicating patient receipt of a procedure, patient need of a procedure, or both. Whether or not a patient needed or received a procedure proved to be valuable prognostic information in our model. However, having sufficient time information to categorize all patients into delay categories would maximize the prognostic value of time to care data.

Second, differential levels of missing data prevented us from applying the same categories to each of our time to care variables. From a machine learning perspective, having equivalent categories across variables is of no concern. With machine learning algorithms, we only care about how well a piece of information can predict an outcome; not how an algorithm uses information to predict an outcome. However, from a feasibility perspective, user-friendliness, and therefore consistency, is paramount. Having equivalent care delay categories across all time to care variables may be more attractive to physicians using our model to inform clinical judgment.

Third, we were not able to validate our model on an external population. External validation is necessary to assess the generalizability of our prognostic model. Without an external dataset on which to test our model, we could not assess its applicability to areas outside of Tanzania's Kilimanjaro region.

5. Conclusion

Understanding the burden of care delays and their impact on injury patient outcomes is essential to improving the quality of trauma care in LMICs. This study provides insight into the burden of care delays and their impact on outcomes among TBI patients presenting to a national referral hospital in Tanzania. Although patients were seen in a timely manner consistent with SATS and standards observed in HICs, care delays were not strongly associated with outcomes. Rather, associations with outcomes persisted primarily among variables indicating need for a procedure or receipt of a procedure. Given the limitations of our data, further research should continue investigating links between care delays and poor outcomes among injury patients in LMICs.

Although our analysis of care delays revealed mostly null associations, the prognostic model presented in this study demonstrates the value of time to care data. Our model is the first to use machine learning and time to care data among a sample of TBI patients from sub-Saharan Africa. Furthermore, incorporation of time to care data into our model improved prediction performance. More importantly, time to care variables comprised the top predictors of a poor outcome in each of our three best performing models. Consequently, the value of time to care data with regard to patient prognosis cannot be understated. Clinical decision support tools using time to care data to inform prognosis may not only improve predictions, but also allow physicians to periodically update patient prognosis during every step of care.

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