A Big-Data Variational Bayesian Framework for Supporting the Prediction of Functional Outcomes in Wake-Up Stroke Patients

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Abstract. Prognosis in Wake-up ischemic stroke (WUS) is important for guiding treatment and rehabilitation strategies, in order to improve recovery and minimize disability. For this reason, there is growing interest on models to predict functional recovery after acute ischemic events in order to personalize the therapeutic intervention and improve the final functional outcome. The aim of this preliminary study is to evaluate the possibility to predict a *good functional outcome*, in terms of modified Rankin Scale (mRS $\leq$ 2), in thrombolysis treated WUS patients by Bayesian analysis of clinical, demographic and neuroimaging data at admission. The study was conducted on 54 thrombolysis treated WUS patients. The Variational Bayesian logistic regression with Automatic Relevance Determination (VB-ARD) was used to produce model and select informative features to predict a *good functional outcome* (mRS $\leq$ 2) at discharge. The produced model showed moderately high 10 $\times$ 5-fold cross validation accuracy of 71% to predict outcome. The sparse model highlighted the relevance of NIHSS at admission, age, TACI stroke syndrome, ASPECTs, ischemic core CT Perfusion volume, hypertension and diabetes mellitus. In conclusion, in this preliminary study we assess the possibility to model the prognosis in thrombolysis treated WUS patients by using VB ARD. The identified features related to initial neurological deficit, history of diabetes and hypertension, together with necrotic tissue relate ASPECT and CTP core volume neuroimaging features, were able to predict outcome with moderately high accuracy.

Keywords: Variational Bayesian inference · Automatic relevance determination · Modeling · Wake-up ischemic stroke · Neuroimaging

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O. Gervasi et al. (Eds.): ICCSA 2020, LNCS 12249, pp. 992–1002, 2020.
https://doi.org/10.1007/978-3-030-58799-4_71

1 Introduction

Worldwide, cerebrovascular ischemia is one of leading causes of disability and death among elderly population [1]. Wake-up Stroke (WUS) represents around a quarter of acute ischemic stroke events [2, 3]. The etiology of ischemic strokes is due to either a thrombotic or embolic event that causes a cerebral brain vessel occlusion and consequent decrease in blood flow to the brain. Nowadays, ischemic stroke is highly treatable using thrombectomy and intravenous thrombolysis reperfusion therapies in selected patients [2]. Neuroimaging plays an important role in patient selection for reperfusion therapy [4]. Recent trials and studies, reported that thrombolysis is safe and efficacious in WUS in patients selected by perfusion neuroimaging [3, 5, 6]. CT perfusion (CTP) is very helpful in determining the necrotic core areas, as well as the extent of hypoperfused tissue that can recover [7, 8], allowing eligibility the reperfusion treatment in wake-up stroke cases [5, 6, 9].

Early prognosis in acute ischemic stroke is important for guiding treatment and rehabilitation strategies, in order to improve recovery and minimize disability [10]. The modified Rankin Scale (mRS) is a commonly used scale to measure the degree of disability or dependence in daily activities of people with neurological and non-neurological disability owing to stroke or other causes [11]. It has become the most widely used clinical outcome measurement for stroke clinical trials [11–13]. mRS ranges from 0 to 6, from perfect health without symptoms to death. The mRS is a 6-point disability scale with possible scores ranging from 0 to 5, from perfect health without symptoms to high disability, with a separate category of 6 for patients who died. Good outcome following stroke is commonly defined as scores 0–2.

Various clinical, demographic and neuroimaging prognostic markers, such as age, clinical severity at admission or infarct size, were associated with functional outcome [10]. Nevertheless, prediction of post-stroke outcome is still challenging since there is large inter-patient variability.

Different machine learning methods can be applied to investigate the possibility to produce a model for predicting functional outcome. However, a high number of predictive features can lead to overfitting. To overcome this problem, a technique like variational Bayes automatic relevance determination (VB-ARD) that eliminates irrelevant features is preferable.

The aim of this preliminary study is to evaluate the possibility to predict a *good functional outcome* (mRS $\leq$ 2) in thrombolysis treated WUS patients by Bayesian analysis of clinical, demographic and neuroimaging data at admission.

2 Materials and Methods

2.1 Study Protocol

The study was conducted on 54 WUS patients (25M/29F; age 72 $\pm$ 9 years) admitted to the Stroke Unit of the University Medical Hospital of Trieste, Italy. We included subjects with acute ischemic stroke developed at morning awakening, admitted within 4.5 h, assessed with CTP within 4.5 h and subsequently underwent thrombolysis

treatment if eligible. No age limit was applied and both genders were included in the study sample. We excluded patients with previous brain lesions and hemorrhagic strokes. Stroke mimics cases were excluded by a complete diagnostic work-up including clinical and CT or MRI follow-up assessment.

All patients received standardized clinical and diagnostic assessment, during admission and at discharge. Non-enhanced CT (NECT), Angio-CT, CT Perfusion neuroimaging work-up was performed at admission in all subjects. Patients eligible for thrombolysis were treated with standard dose of intravenous rtPA (0.9 mg/kg of body weight, maximum of 90 mg, infused over 60 min with 10% of the total dose administered as an initial intravenous bolus over 1 min).

The study was approved by the Local Ethics Committee and conducted in line with the principles of the Declaration of Helsinki. All participants released their informed consent to participate in the study.

2.2 Dataset

2.2.1 Demographic and Clinical Data

The following demographic and clinical data at admission were collected for each included patients: (1) age (y); (2) sex (M/F); (3) Stroke severity measured by National Institutes of Health Stroke Scale (NIHSS) score at admission [14] (4) premorbid and discharge mRS [11]; (5) Lesion side (Left/Right); (6) stroke risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, ischemic cardiopathy, atrial fibrillation); (7) Stroke syndrome by Bamford classification [15] (Total Anterior Circulation Infarct, TACI; Partial Anterior Circulation Infarct, PACI; Lacunar Stroke, LACI; Posterior Circulation Infarct, POCI); (8) Stroke etiology by TOAST classification [16] (Atherothrombotic, Lacunar, Cardioembolic, Cryptogenic, other cause); (9) Time from last seen well to admission; (10) Time from admission to thrombolysis treatment.

2.2.2 Neuroimaging Data and CTP Processing

All patients underwent a standardized CT protocol at admission consisting of NECT, CTA, and CTP. NECT performed with a 256 slice CT scanner (Brilliance iCT 256 slices, Philips Medical Systems, Best, Netherlands) at the Radiology Department of the University Medical Hospital of Trieste (Italy). The Alberta Stroke Program Early CT Score (ASPECTS) was used to quantify the amount of ischemia on NECT [17]. CTP acquisition involves intravenous injection of contrast medium and acquisition of three-dimensional axial acquisitions on a whole brain volume every 4 s, resulting in a total scanning time of 60 s. CTP source image processing was performed by using Extended Brilliance Workstation v 4.5 (Philips Medical Systems, Best, Netherlands) and in-house code developed in Matlab (MathWorks Inc., Natick, MA), as previously described [18, 19]. The perfusion maps mean transit time (MTT), cerebral blood volume (CBV) and cerebral blood flow (CBF) were calculated. Ischemic core and penumbra areas were identified by application of specific thresholds [20]. Ischemic core volume as well as total hypoperfused volume including core and penumbra regions, excluding artifacts was calculated with an algorithm described in a previous study [18]. Core/penumbra mismatch was calculated as a ratio between penumbra volume and total hypoperfused volume. CTP processing is summarized in Fig. 1.

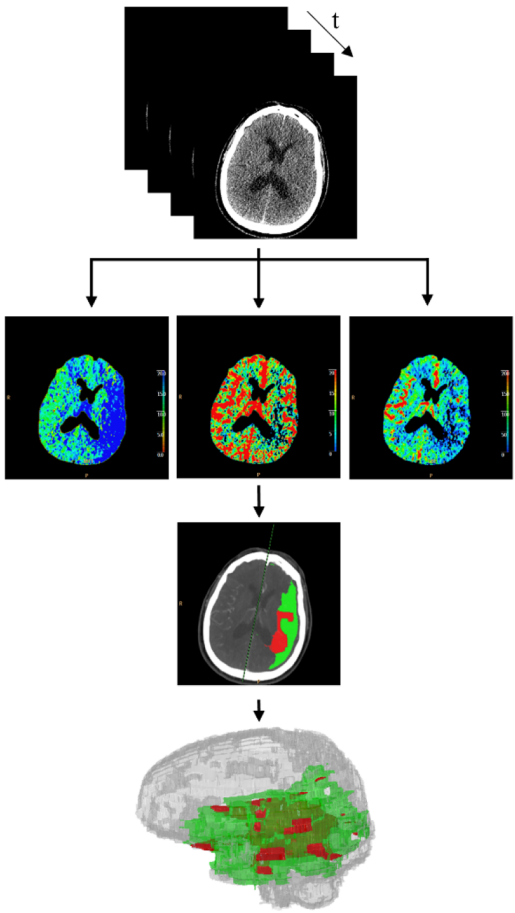


Fig. 1. CTP processing summary. From top to bottom: Source CTP data; MTT, CBV and CBF calculated maps, from left to right, respectively; core (red)/penumbra (green) summary map; 3D representation of total hypoperfused volume (core + penumbra). (Color figure online)

2.2.3 Outcome Measure

The mRS, an ordinal scale with 7 categories ranging from zero (no symptoms) to 6 (death), was the outcome measure: 0) No symptoms at all; 1) No significant disability despite symptoms; able to carry out all usual duties and activities; 2) Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance; 3) Moderate disability; requiring some help, but able to walk without assistance; 4) Moderately severe disability; unable to walk and attend to bodily needs without assistance; 5) Severe disability; bedridden, incontinent and requiring constant nursing care and attention; 6) Dead. Good outcome class was defined with mRS $\leq$ 2, while bad outcome class with mRS > 3.

2.3 Data Pre-processing and Classification

In this study, we used a dataset consisting of all aforementioned demographic, clinical and neuroimaging features. The dataset was preprocessed before the analysis. Considering that the dataset variables were measured in different units, each variable was normalized by subtracting the mean from each variable and then divided by its standard deviation [21].

In this work, we used Variational Bayesian logistic regression with Automatic Relevance Determination (VB-ARD) [22] to select informative features and produce a sparse model to predict a *good functional outcome* (mRS $\leq$ 2) in thrombolysis treated WUS patients.

Given some data $D = \{X, Y\}$ where $X = \{x_1, \ldots, x_N\}$ and $Y = \{y_1, \ldots, y_N\}$, $N = 54$ subjects are input/output pairs. The length of each x_n input vector is 27, corresponding to the number of features, and y_n is the output class ($y_n = 1$ for good outcome mRS 2 and $y_n = -1$ for bad outcome mRS > 3).

This approach has an advantage over some regularization methods which require a separate validation set to prune less relevant features. Furthermore, this method produces a posterior distribution allowing us to build the varying-intercept sparse feature model. The methodology applied here is similar to the one proposed by Bishop (2006) [23] with a different implementation of Automatic Relevance Determination (ARD). Instead of using type-II maximum likelihood [24–26], where the parameters are tuned by maximizing the marginal likelihood, here we applied full Bayesian treatment [22]. The basic generative model corresponds to the one used in Bishop (2006) [23], and the prior is selected to be non-informative, modelled by a conjugate Gamma distribution [22]. The posterior probability distribution of the model parameters conditionally upon the predictors has been obtained by Variational Bayesian inference that is based on maximizing a lower bound on the marginal data log-likelihood [22, 27]. The obtained distribution allows us to find the inverse of the predictors' covariance matrix (precision matrix) and apply Automatic Relevance Determination that consists of assigning an individual hyper-prior to each regression coefficient independently determining how relevant each of them is.

The ability of a produced model to predict accurately the outcome was validated with 10 times 5–fold cross-validation. Finally, the average accuracy over 50 runs was calculated.

3 Experimental Results

Summary of patient's demographic and clinical data at admission, as well as neuroimaging findings are reported in Table 1.

Table 1. Demographic, clinical characteristics and neuroimaging findings at admission. Data are presented as Means ± SD, Medians (IQR) and frequencies.

Patient's characteristics	N = 54
Age [y]	72 ± 9
Sex F: M [n]	29: 25
Last time seen well - Admission [min]	509 (364–702)
Admission - Thrombolysis [min]	68 (52–140)
ASPECTS	10 (10–10)
NIHSS at baseline	7 (5–14)
Pre-morbid mRS	0 (0–0)
Lesion side L: R [n]	28: 26
Bamford stroke subtypes [n (%)]	
TACI	13 (24%)
PACI	27 (50%)
LACI	5 (9%)
POCI	9 (17%)
TOAST classification [n (%)]	
Atherothrombotic	9 (17%)
Lacunar	5 (9%)
Cardioembolic	22 (41%)
Cryptogenic	18 (33%)
Other cause	0 (0%)
CTP parameters	
Mismatch	1.0 (0.9–1.0)
Total hypoperfused tissue [ml]	16.2 (2.5–79.6)
Penumbra [ml]	15.1 (2.6–71.2)
Core [ml]	0 (0–3.8)
Stroke risk factors [n (%)]	
Hypertension	35 (65%)
Diabetes mellitus type II	9 (17%)
Dyslipidemia	39 (72%)
Smoking	11 (20%)
Obesity	6 (11%)
Atrial fibrillation	21 (39%)
Ischemic cardiopathy	14 (26%)

VB-ARD produced a sparse model and as a result the following features were selected: (1) NIHSS at admission, (2) Age, (3) TACI stroke syndrome, (4) ASPECTs, (5) Core CTP volume as well as presence of risk factors as (6) arterial hypertension and (7) diabetes mellitus type II. Posterior means and their standard errors for selected model features are reported in Table 2. The overall accuracy of the identified model was 71%.

Table 2. Posterior means and their standard errors for model features.

	Posterior mean	Posterior standard error
NIHSS at admission	−1.126	0.009
Age	−0.595	0.005
TACI	−0.426	0.007
ASPECTS	0.304	0.006
Hypertension	−0.234	0.005
Diabetes mellitus type II	−0.212	0.004
Core Volume	−0.101	0.007

4 Discussion

The last decade has seen a substantial increase in the amount of collected health-related data and significant progress has been made in technologies able to analyze and understand this data. This is correlated to the emerging *big data* context [28] and to the increasing focus on the definition of a *big data analytics* methodologies [29–31] as well as to the *big data* privacy and security aspects [32, 33]. In recent years there is growing interest on the role of *big data* in healthcare and stroke [34, 35], as well as on markers and models to predict functional recovery after acute ischemic events in order to personalize the therapeutic intervention and improve the final functional outcome [10, 36].

Currently, there is no study on clinical features and models to predict functional outcome measured by mRS in thrombolysis treated WUS patients. Bayesian techniques are becoming very popular in the field of data analysis in medicine [37–39]. In this preliminary study we proposed a method based on Bayesian inference for functional outcome prediction in terms of mRS in WUS as a challenging subtype of stroke.

The Bayesian analysis produced a sparse predictive model which exhibited moderately high accuracy 71% in WUS treated patients, highlighting the importance of NIHSS at admission, age, TACI stroke syndrome, ASPECTs, core CTP volume as well as presence of risk factors as arterial hypertension and diabetes mellitus type II.

The obtained model confirmed the important impact of stroke severity measured by baseline NIHSS, TACI stroke syndrome and age on discharge outcome. The severity of stroke on neurological examination and age are probably the most important factor affecting short- and long-term outcome [16, 40, 41]. As a general rule, large strokes, manifested usually as a TACI syndrome with severe initial clinical deficits, have poor outcomes compared with smaller strokes [42]. Recent studies showed that patients with diabetes mellitus type II and arterial hypertension are generally characterized with poor outcome [43, 44].

CTP core volume and ASPECTS neuroimaging features contributed to the prediction of mRS outcome. ASPECTS was found as a strong method for predicting functional outcome in thrombolysis treated acute ischemic stroke patients compared to valuation of clinical characteristics alone [45]. CTP infarct core volume and collateral grade were reported as strongest predictors of a good 3 months mRS outcome

following reperfusion treatment in patients admitted within 4.5 h from symptom onset [46, 47]. Although the total ischemic CTP volume didn't result as direct predictor, it participates indirectly through its contribution to NIHSS at admission [18] and TACI syndrome. A recent WUS CTP study showed that CTP core volume, NIHSS at admission and ASPECTS predict NIHSS at 7-days, while total hypoperfused volume and core volume on CTP predict infarct lesion volume at follow-up CT [48].

5 Conclusions and Future Work

In this study Variational Bayesian logistic regression with Automatic Relevance Determination produced a sparse model selecting informative features to predict a *good functional outcome* in thrombolysis treated WUS patients. This approach has an advantage over some regularization methods which require a separate validation set to prune less relevant features. Indeed, time last seen well to admission was not associated with functional outcome at discharge supporting the hypothesis that neurological assessment, comorbidities together with the advanced neuroimaging are more important than the influence from time to admission. The main limitation of this pilot study is limited single center sample size, mild/moderate stroke severity and prevalence penumbra compared to ischemic core on CTP in our cohort.

In conclusion, in this preliminary study we assessed the possibility to model the prognosis in thrombolysis treated WUS patients by using VB-ARD. The identified features related to initial neurological deficit, history of diabetes and hypertension, together with necrotic tissue related ASPECT and CTP core volume neuroimaging features, were able to predict outcome with moderately high accuracy. Future work will be mainly focused to improve the actual framework.

Acknowledgements. This study was partially supported by Master in Clinical Engineering, University of Trieste. A. Miladinović is supported by the European Social Fund (ESF) and Autonomous Region of Friuli Venezia Giulia (FVG).

Conflict of Interest. The authors have no conflict of interest do declare.

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