Prognostic models for ambulatory recovery functions in acute ischemic stroke patients with thrombolysis therapy

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Abstract

Background. The purpose of this study was to develop models to predict the recovery of ambulatory functions taking into account the capability of the motor system to functionally reorganize in response to thrombolysis therapy.

Methods. We predicted ambulatory functions recovery using retrospective data from a stroke registry of acute ischemic stroke patients who received thrombolysis therapy. Multivariate regression was used to construct the models. Multicollinearity and significant interactions were examined using variance inflation factors, while a Cox & Snell classification were applied to check the fitness of each model.

Results. The models correctly predicted clinical variables that were associated with an improvement or non-improvement in functional ambulatory outcome. Broca's aphasia (OR = 2.270, P = 0.002, CI =1.34-3.83) was associated with improved functional outcome at discharge, while patients aged 80 years or older (OR = 0.942, P = <0.001, CI =0.92-0.96), patients with congestive heart failure (OR = 0.496, P = 0.040, CI = 0.25-0.97), higher NIHSS (OR=0.876, P = 0.001, CI = 0.80-0.95), taking antihypertensive medication (OR = 0.436, P = 0.023, CI = 0.21-0.89) were not associated with improved ambulatory functional outcome with thrombolysis. The discriminating ability for the model was 74.2% for the total population, 71.7% for the rtPA group, and 72.2% for the no-rtPA group indicating strong performance.

Conclusion. Prognostic models that can predict improved functional ambulatory outcome in thrombolysis therapy can be beneficial in the care of stroke patients. Our models predicted improved functional recovery of Broca's aphasia after thrombolysis therapy, suggesting a future potential to evaluate motor speech area after stroke.

Background

Predictive models for the risk of stroke have been helpful to guide evaluations and the development of interventions for a stroke event[1]. Since the heterogeneity of stroke provides a source of variability that should be amenable to clinical and motoric parsing, the accurate prediction of motoric recovery, especially in the patient's daily life ambulatory activities before and after recovery, represents a strong tool to evaluate functional outcome. Moreover, stroke is a common etiology for physical immobility [2], and motoric recovery would represent a suitable cut-off assessment based on direct evaluation of daily life mobility before and after treatment and recovery.

Recent guidelines from the American Heart Association (AHA) suggested the importance of considering outcome variables that capture the wide variation in treatment outcomes, primarily to assess recovery following thrombolysis therapy [3]. A clinically relevant variable that captures the complex abnormalities that underlie ischemic stroke is also necessary to assess functioning outcome. Such a variable is expected to reflect the wide variation in a stroke patient baseline abnormality and provide clinical information regarding the state of a patient's recovery [3-8]. Treatment outcome with recombinant tissue plasminogen (rtPA) varies significantly across stroke patients with the same diagnosis. Motoric impairment also varies widely and represents a prominent complicated abnormality after stroke [9]. As the patient's daily life ambulatory activities changes especially before and after recovery, an ambulatory model to predict clinically relevant differences before and after treatment of acute ischemic stroke can increase the capability to detect functional outcome. For example, the recovery of upper and lower limbs or other motor impairments after thrombolysis therapy may predict the degree of recovery in the affected corticospinal tract (CST) or other motoric pathways after stroke [10]. Indeed, this could indirectly assess the role that thrombolysis plays in interacting with the neurobiological mechanisms for the recovery of ambulatory functions after treatment and before rehabilitation. This is important in the clinical assessment of patients following thrombolysis therapy.

The degree in the impairment of ambulatory activities is an important indicator for prognosis. This is because the initial degree of damage may predict a poor or good ambulatory functional recovery[11]. In this study, we developed multivariate models to predict the recovery of ambulatory functions 14 days after stroke recovery. We determined whether specific baseline clinical risk variables are associated with an improvement or non-improvement in ambulatory recovery functions following thrombolysis therapy. First, we evaluated the demographic and clinical variables associated with thrombolysis therapy at the population level. Second, we analyzed baseline characteristics for improved or non-improved ambulatory functions in rt-PA treated or non-treated acute ischemic stroke patients. This allowed us to develop ambulatory models for functional outcome directly linked to daily life motoric activities in the whole stroke population, rtPA-treated stroke patients and in acute ischemic stroke patients excluded from thrombolysis therapy.

Methods

2.1 *Research Design*

This study contains retrospective data obtained from the Greenville Health Care System (GHS) stroke registry. The data is retrospective data analysis and patients' data were de-identified. Data within the GHS stroke registry has been standardized according to the Get With The Guidelines (GWTG)-Stroke registry formed by the American Heart Association (AHA) and American Stroke Association (ASA) in a joint effort to enhance the quality of care provided to patients with a diagnosis of acute stroke or transient ischemic attack [12]. Our analysis was conducted on anonymous subjects using retrospective data from a regional stroke center's registry and consents were obtained for all participants following 14 days of stroke recovery. The registry has been described in previous studies [13-15]. Our data analysis complies with the STROBE guidelines for cohort studies [16]. Eligibility for rtPA was based on the AHA inclusion guidelines for early management of patients with acute ischemic stroke [17, 18], and all cases of stroke were confirmed by computed tomography (CT). All data including neuroimaging data were reviewed by a clinician, who determined whether the patient met the clinical case description of acute stroke. A stroke nurse identified and abstracted data for the patients' demographics and clinical variables that were used for the study. Identified clinical variables include: coronary artery disease (CAD), carotid stenosis, diabetes, dyslipidemia, atrial fibrillation/flutter, congestive heart failure (CHF), hypertension, previous stroke or transient ischemic attack (TIA), smoking history, peripheral vascular disease (PVD), and neurological status at presentation. Independence of ambulation was evaluated and used to develop a model for functional outcome. Ambulatory ability prior to current event, at admission, and at discharge were determined. Patients were assigned a score 0-3 based on the following possible respective outcomes: undocumented (0), unable to ambulate (1), able to ambulate with assistance (2), and able to ambulate independently (3). Changes in ambulation were tracked from admission to discharge to evaluate potential risks and benefits of rtPA therapy in stroke patients. The validity of the scoring has been described in a previous study[19].

2.2 Data Analysis

The SPSS Statistics Software version 15.0 (Chicago, IL) was used for all statistical analyses and $P<0.05$ was used to establish statistical significance in all comparisons. The patients' data was stored in a de-identified manner and patients were divided into groups based on if they were administered rtPA (rtPA group) or if they were excluded from rtPA (no rtPA group). Descriptive statistics were calculated for the demographic and clinical characteristics of patients in these groups. For all continuous variables, the mean, standard deviation, and range were calculated. Comparisons between the rtPA group and the no-rtPA group were determined using two-tailed, independent samples, Student's T-tests. For all discrete variables, the number of patients and percentage of patients in that category were calculated while a Pearson's Chi-Squared analysis was used for categorical variables. Comparisons between groups were made using Pearson's Chi-Squared analyses.

Logistic regression models were developed to predict improved functional outcome based on ambulation in rtPA and no-rtPA groups. Models were developed for, 1) the total stroke population (rtPA and no rtPA group), 2) sub group with no rtPA and 3) the rtPA sub group. The models were established using steps drawn from multivariate Cox model [20] method for selecting independent variables that indicate the "best" model. First, we performed univariate analysis for each variable to initiate the selection process. Second, we considered a variable with p value less than 0.05 for inclusion in our multivariate models [21]. Third, we entered selected variables into our multivariate model. For variables that showed high collinearity, interactions between independent variables were examined using variance inflation factors to confirm independence of variables included in regression model. A variable was excluded from the multivariate model if its p value was greater than 0.05. We adjusted for confounding factors to control the confounding effects of specific demographic and clinical variables. Lastly, after establishing a multivariate main effect model, the validity of our models was tested using a Hosmer-Lemeshow test, while the overall correct classification percentage, and the area under the Receiver Operating Curve for score prediction was determined. In the final models, predicted parameters were estimated with standard errors, odds ratios, and all variables were calculated with a 95% asymptotic confidence interval. We cross-validated our analytical methods to internally validate our resulting predictive models. To cross-validate, we used 500 samples to compute permutation testing and establish the statistical significance of the predictions [22]. Since the analysis was intensive, we narrowed the computation to the models that best predicted the primary outcomes in our sample.

Results

Of the 1,446 patients eligible to receive rtPA, 595 were treated with thrombolytic therapy, while the remaining 851 were excluded. Characteristics of patients that received rtPA versus those excluded and with improved or non-improved functional outcome are presented in Fig 1. Patients treated with rtPA were significantly younger than patients in the no rtPA group (65.7yr ± 15yr and 70yr ± 14.7yr, respectively) and were less likely to have a history of atrial fibrillation/flutter, carotid artery stenosis, CHF, previous stroke, and were more likely to smoke. Moreover, patients treated with rtPA were less likely to ambulate independently upon admission, had higher NIH stroke scale scores, and were more likely to present with weakness/paresis or Broca's aphasia/language disturbance as an initial examination finding. The rtPA group was more likely to be transported to the hospital by Emergency Medical Services (EMS) as opposed to private transportation or transfer from another hospital. Therefore, patients receiving rtPA predominantly received care at the Emergency Department. There was no statistically significant difference between rtPA administration between Caucasian and African-American patients; however, patients of Hispanic ethnicity were more likely to receive rtPA than those of non-Hispanic ethnicity.

To predict rtPA with improved outcome and rtPA without improved outcome the regression model was developed. The final model considered all significant variables shown in Table 1; the result is expressed in Table 2. Patients with no improvement following rtPA were more likely to be over the age of 80 (OR = 0.967, P = <0.001, CI = 0.97-0.99), present with atrial fibrillation (OR = 0.668, P = 0.024, CI = 0.47-0.94), carotid artery stenosis (OR= 0.511, P = 0.023, CI = 0.29-0.91), a history of previous stroke (OR = 0.479, P = <0.001, CI = 0.36-0.65), with a calculated risk of mortality GWTG (OR = 0.933, P = 0.014, CI = 0.88-0.99), or with an increased time from symptom onset to presentation (OR = 0.993, P = <0.001, CI = 0.99-0.995). Patients more likely to be associated with an improved functional ambulatory outcome following rtPA were more likely to be Hispanic in ethnicity (OR = 2.808, P = 0.034, CI = 1.08-7.30), present with moderate stroke indicated by calculated NIHSS (OR = 1.112, P = <0.001, CI = 1.06-1.17), present with weakness/paresis (OR = 1.796, P = 0.005, CI = 1.19-2.71), Broca's aphasia (OR = 1.571, P = 0.003, CI = 1.16-2.12), hypertension, or present with hypertension and are receiving antihypertensive medication (OR = 1.530, P = 0.034, CI = 1.03-2.26). The ROC curve is presented in Fig 2, indicating that 74.2% of the total population were correctly classified.

For the subset of the no rtPA group, four factors were associated with a non-improved functional outcome: age greater than 80 years old (OR = 0.961, P = <0.001, CI = 0.95-0.98), female gender (OR = 0.686, P = 0.028, CI = 0.49-0.96), previous stroke (OR = 0.538, P = 0.002, CI = 0.37-0.79), and NIHSS (OR = 0.899, P = 0.005, CI = 0.83-0.97). However, atrial fibrillation (OR = 2.133, P = 0.001, CI = 1.34-3.83) was the only factor found to be associated with improved functional outcome at discharge (Table 3). The area under the curve (AUROC) indicates 72.2% (95% CI, 0.6715 - 0.7718) of accurate classification, suggesting a very good fit for the multivariate model as shown in the discriminating ability of the model (Fig 3).
For patients that received or included for rtPA, five factors were predicted to be associated with their functional outcomes. Presentation of Broca's aphasia (OR = 2.270, P = 0.002, CI =1.34-3.83) was associated with improved functional outcome. Contrarily, stroke patients older than 80 years of age (OR =

0.942, P = <0.001, CI =0.92-0.96), and patients with congestive heart failure (OR = 0.496, P = 0.040, CI = 0.25-0.97), calculated higher NIHSS (0.876, P = 0.001, CI = 0.80-0.95), and patients taking antihypertensive medication (OR = 0.436, P = 0.023, CI = 0.21-0.89) were associated with a no improvement in functional outcome (Table 4). The discriminating ability of the model was strong as shown by the ROC (Fig 4), with area under the curve (AUROC) of 71.7% (95% CI, 0.6639 - 0.7710).

Discussion

Living an independent life after stroke depends mainly on the recovery of all motor functions. Therefore, an accurate prediction of motor recovery for stroke patients most likely to benefit from thrombolysis therapy will help clinicians to plan rehabilitation programs and set realistic goals. In this study, we used regression models to predict ambulatory recovery in stroke patients with thrombolysis therapy. The goal is to identify demographic and clinical variables that contribute to functional ambulatory outcome following thrombolysis therapy. This approach provides the opportunity to predict the recovery of ambulatory functions after stroke to help in the selection of appropriate motor rehabilitation strategies for individual patients on the basis of the integrity of the motor system and its capability to functionally reorganize.
In our results, patients with Hispanic ethnicity, stroke severity (based on calculated NIHSS), presentation of weakness/paresis, Broca's aphasia and with a history of receiving antihypertensive medication were more likely to be associated with an improvement in ambulatory outcome after rtPA. Furthermore, our model predicted the independent prognostic role of increasing age on rtPA and functional outcome. It seems likely that this could account for the prediction of a no improvement in the ambulatory status with rtPA in patients > 80 and 85 years of age. Since elderly octogenarian and nonagenarian patients had a higher risk of subsequent complications, our model predicted lower chances to recover from their stroke. Our finding is consistent with observational studies in which octogenarians and nonagenarians have lower chances of achieving favorable outcomes than patients <80 [23-26]. The non-improved or poor ambulatory outcomes may partly reflect the numerous comorbidities of elderly patients [27] as well as their decreased ability to regain motoric functions following thrombolysis therapy [28]. Additionally, our finding of poor or no improvement in functional ambulatory outcomes in patients with congestive heart failure, higher NIH scores and antihypertensive medication agrees with several studies [13, 29-31], where the advanced age subgroups had significantly higher rates of congestive heart failure, ischemic heart disease, and hypertension. In patients that did not receive rtPA, our model predicted poor or no improvement in ambulatory outcomes for patients greater than 80 years of age, patients who presented with atrial fibrillation, carotid artery stenosis, history of previous stroke and calculated risk of mortality GWTG. Precisely, in the adjusted analysis, female stroke patients with age greater than 80 years of age, previous stroke, and atrial fibrillation were associated with a non-improvement in their ambulatory status. These factors are known to influence functional outcome in longitudinal studies and are more frequent in female stroke patients [15, 32-34].

In the total stroke population, patients with Broca's aphasia that received rtPA were more likely to be associated with an improvement in functional ambulatory outcome, and this result was retained in the adjusted analysis for the subset of rtPA group. This finding suggests the role of thrombolysis in the resolution of the initial motoric speech deficits in rtPA-treated patients. Motor impairment including the inability of stroke patients to coordinate movement of the lips, jaw and tongue with specific motor control strategies is a frequent complication associated with stroke and represents an important factor that enhances patient's ability to live an independent lifestyle after stroke[35]. The inter-individual variation in the initial impairment of motor speech and subsequent recovery of function makes it difficult for an accurate prognosis for each patient. Therefore, the accuracy of prediction in the recovery of motor speech might be increased by considering the ability of the motor speech cortical area to functionally reorganize in response to thrombolysis therapy. A major finding in this study is that patients with Broca's aphasia that received rtPA were more likely to be associated with an improvement in motor speech following thrombolysis therapy. This finding suggests an interaction between thrombolysis and the neurobiological mechanisms of recovery for motor speech after treatment and successful recovery.

As a limitation, our models need to be externally validated in an independent sample of patients. For this reason, we are currently working on this validation with a prospective study to correct for case-to-case mix variations in non-randomized acute ischemic stroke populations. Our model only accounts for patients that were treated within the 4.5 hours of thrombolysis therapy and 14 days of recovery. Therefore, there is a need for the development of more models that take into consideration patients treated in 3 to 6 hours of stroke onset and 3 or 6months post recovery. Moreover, a lack of data on mortality may provide inaccurate estimate for the model performance, especially since the internal validation used in this study has a tendency to over evaluate the model fitness. Nevertheless**,** our model represents an important step in the determination of thrombolysis therapy and improved functional recovery of Broca's aphasia after thrombolysis therapy.

Conclusion

Although the evaluation of the integrity of the corticomotor area is not used regularly to make a prognosis, but recent developments in this area have been very interesting. A major strength of this study is the ability to develop models that use daily life motoric activities of stroke patients to predict functional outcomes following thrombolysis therapy. Our models reveal an improved functional recovery of Broca's aphasia after thrombolysis therapy.

Declarations

Ethics approval and consent to participate: This study was performed with the approval of the Institutional Review Board of Greenville Health System and the institutional Committee for Ethics. Being a retrospective data analysis with blinded data.

Consent for Publication: Not applicable.

Availability of data and materials. All materials are available for use from the corresponding author.

Competing Interest : The corresponding auth is an Associate Editor in BMC Neurology

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Authors' contributions. Statistical analysis was performed by JG. Critical interpretation of the results was performed by all authors. The manuscript was drafted by TIN and revised by MS, LB, BB, ZC, and II. All authors have read and approved the manuscript and ensure that this is the case.

Availability of data and materials: Data will be made available on request.

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Tables

Due to technical limitations, the tables have been included as supplemental files below.

Here are the table legends:

Table 1: Clinical, hospital-based factors and patient demographics were compared between rtPA and no rtPA groups. * Indicates statistical significance with a confidence interval of $P < 0.05$.

Table 2: Factors associated with improvement or no improvement in ambulation in total stroke population (rtPA or no rtPA) following an adjustment for the confounding effects of demographics, past medical history, and clinical characteristics as determined by multivariate binary logistic regression and compared. Adjusted OR<1 denote variables more associated with rtPA and no improvement in ambulation while Adjusted OR>1 denote variables more associated with rtPA and improvement in ambulation Multicollinearity and interactions among independent variables were checked. Hosmer-Lemeshow test, Cox & Snell ($R2=0.167$), and Classification table (overall correctly classified percentage =72.2%) were applied to check the model fitness. * Indicates statistical significance with a confidence interval of $P < 0.05$.

Table 3. Factors associated with functional outcome at discharge for the population of patients with no rtPA following an adjustment for the confounding effects of demographics, past medical history, and clinical characteristics as determined by multivariate binary logistic regression and compared. Adjusted OR<1 denote variables more associated with non-improved functional ambulatory outcome while adjusted OR>1 denote variables more associated with improved functional ambulatory outcome. Multicollinearity and interactions among independent variables were checked. Hosmer-Lemeshow test, Cox & Snell ($R2=0.171$), and Classification table (overall correctly classified percentage =71.1%) were applied to check the model fitness.* Indicates statistical significance with a confidence interval of $P < 0.05$.

Table 4. Clinical factors that were associated with functional outcome for acute ischemic that received rtPA. Adjusted analysis was carried to control for confounding effects of demographics, past medical history, and clinical characteristics as determined by a multivariate binary logistic regression and compared. Adjusted OR<1 denote variables more associated with non improvement while adjusted OR<1 denote variables more associated with an improvement. Multicollinearity and interactions among independent variables were checked. Hosmer-Lemeshow test, Cox & Snell ($R2=0.181$), and Classification table (overall correctly classified percentage =74.2%) were applied to check the model fitness* Indicates statistical significance with a confidence interval of $P< 0.05$.

Figures

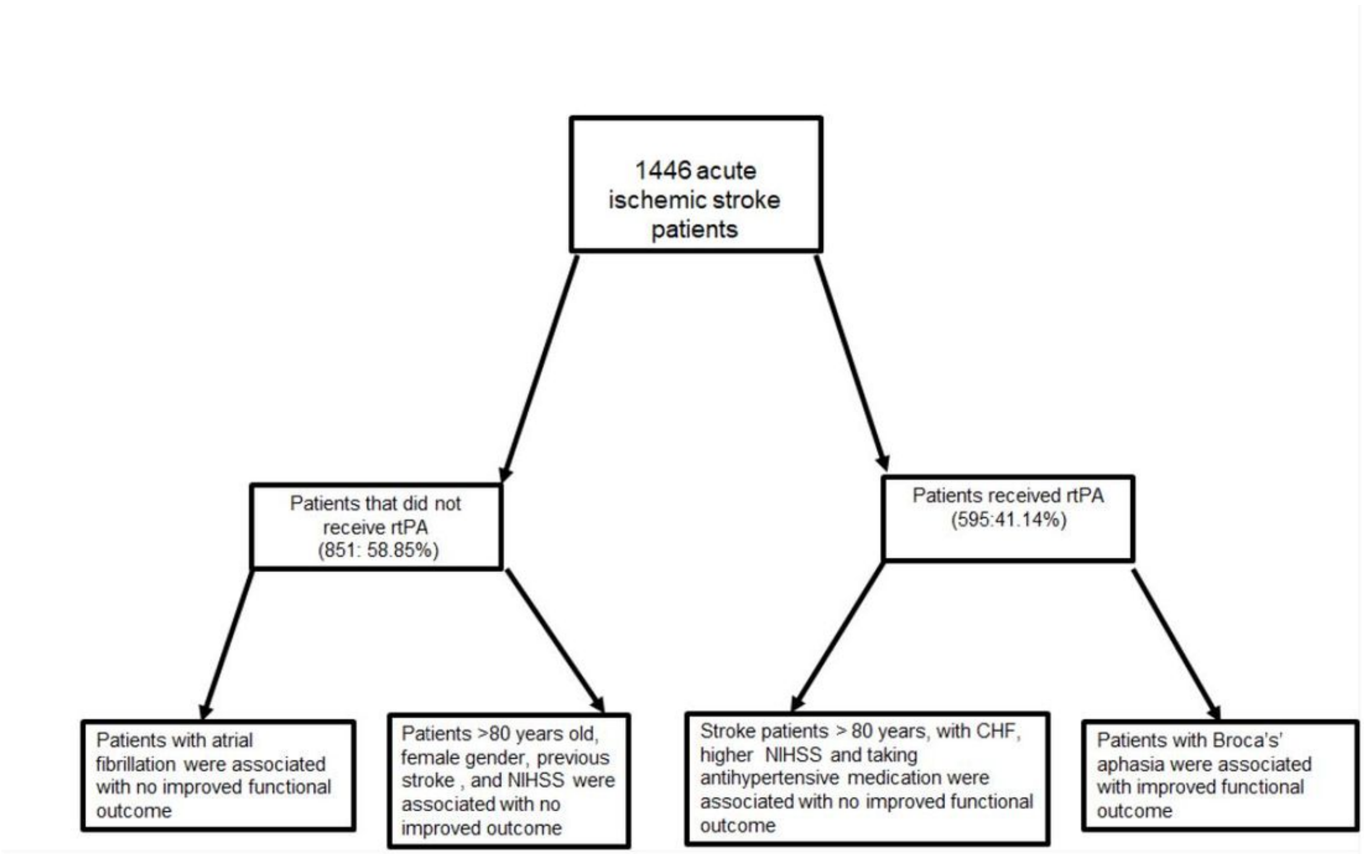

Figure 1

Demographic and clinical characteristics of patients that received rtPA versus those excluded, and with improved or non-improved functional outcome.

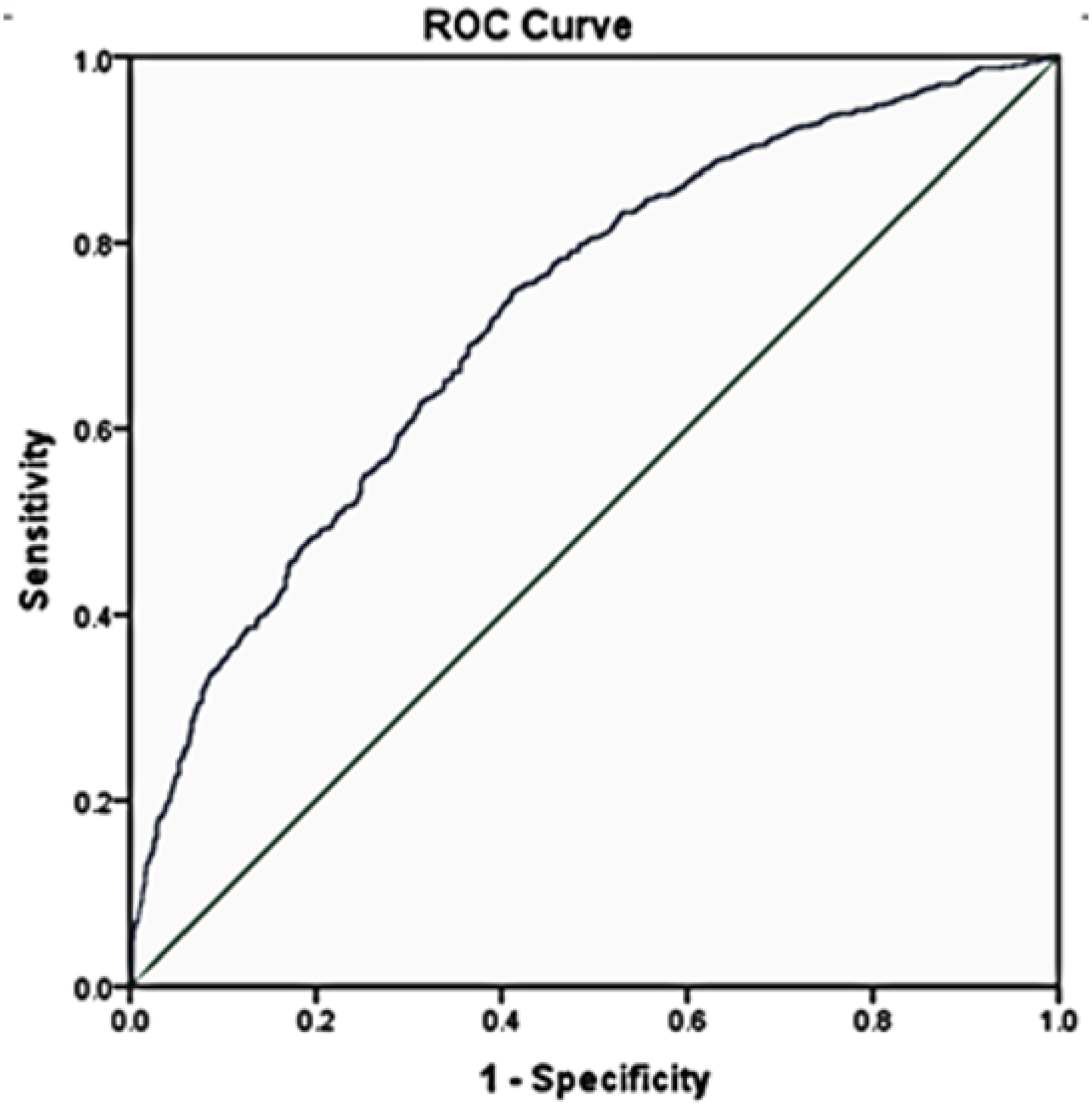

Figure 2

The Receiver Operating Characteristics (ROC) curve for functional outcome in the whole population model. The discriminating ability of the model as shown by the ROC curve indicates a good fit with area under curve (AUROC) of 74.2% for the total population.

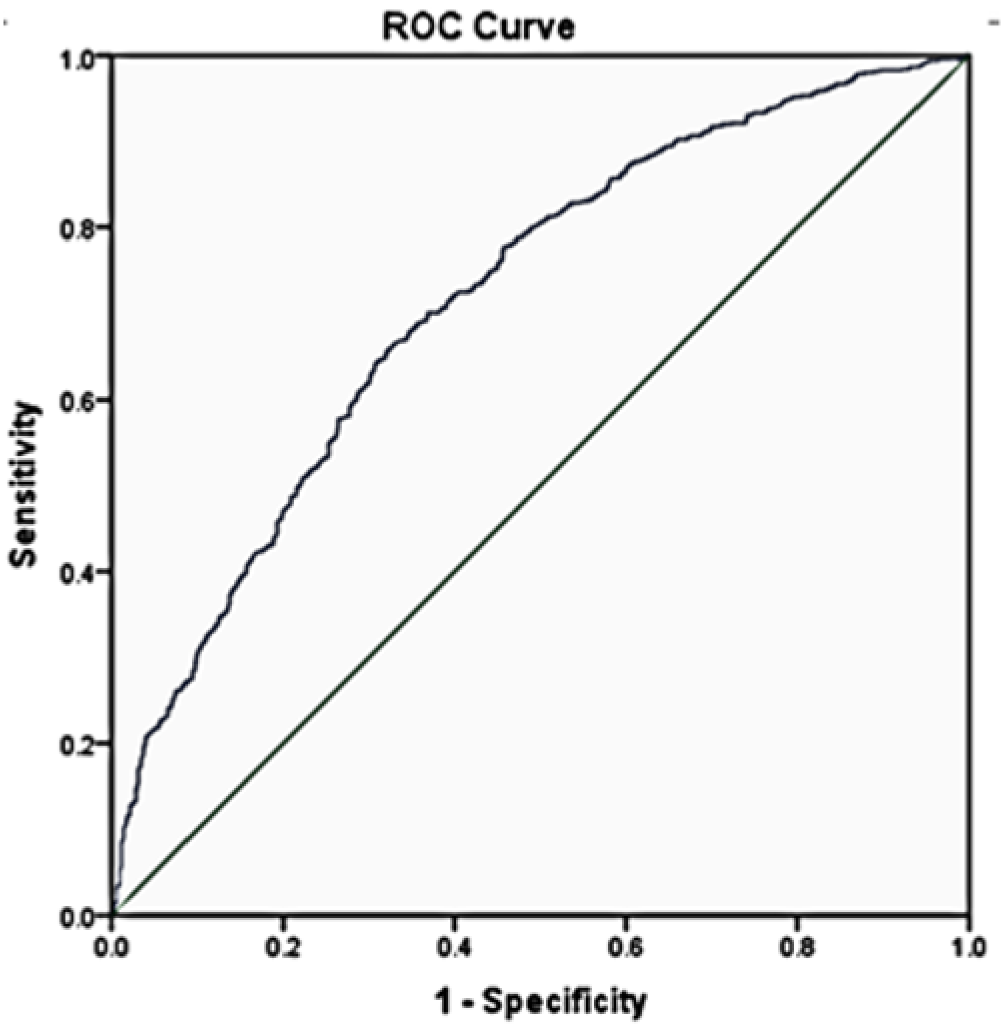

Figure 3

The Receiver Operating Characteristics (ROC) curve for stroke patients excluded from rtPA. The discriminating ability of the model as shown by the ROC curve indicates a good fit with area under curve (AUROC) of 72.2% for the no-rtPA group correctly classified.

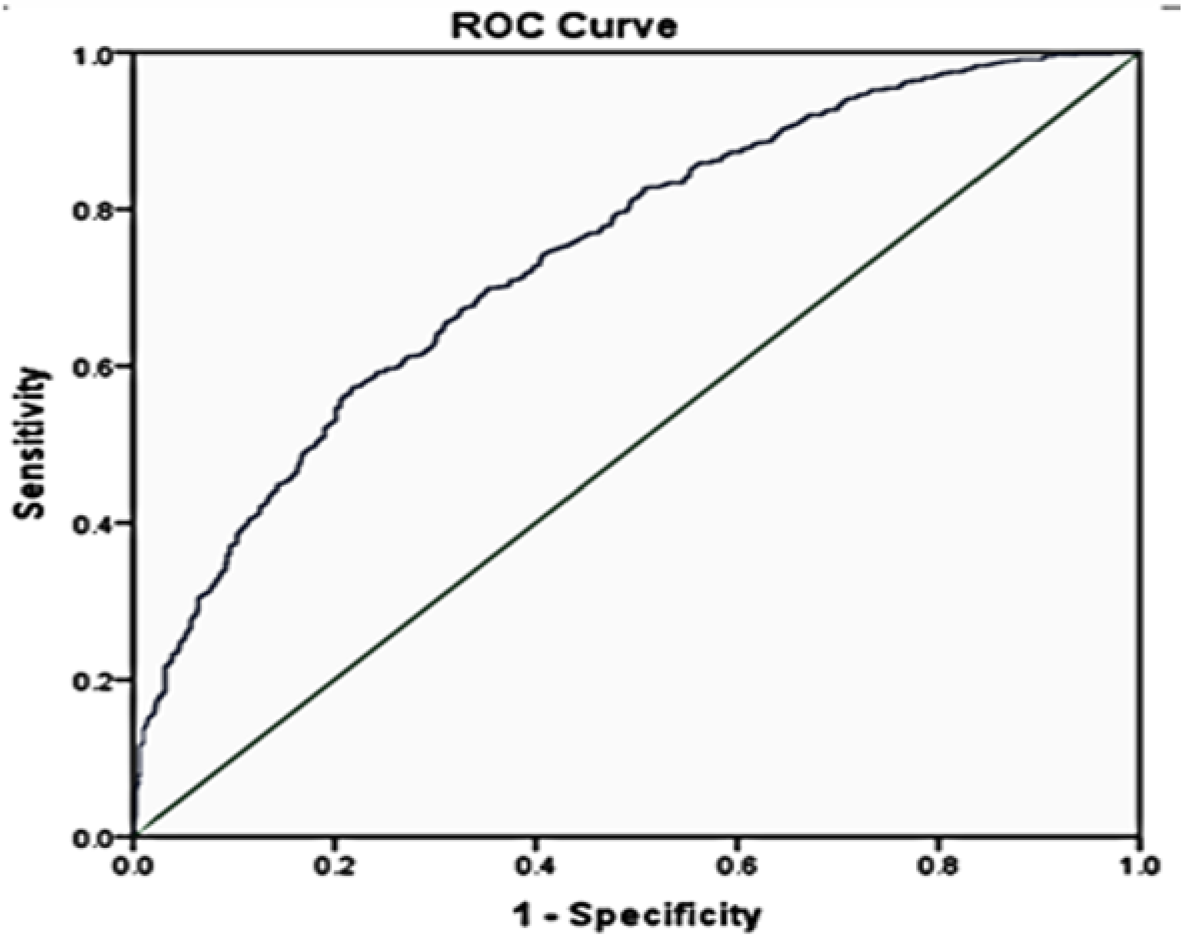

Figure 4

The Receiver Operating Characteristics (ROC) curve for stroke patients that received rtPA. The discriminating ability of the model as shown by the ROC curve indicates a good fit with area under curve (AUROC) of 71.7% for the rtPA group, correctly classified.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.png
- supplement2.png
- supplement3.png
- supplement4.png