Neurology Asia 2020; 25(2) : 109 – 117

Artificial neural network-based analysis of the safety and efficacy of thrombolysis for ischemic stroke in older adults in Taiwan

[1,2,3,4]Chen-Chih Chung, [1,2,4]You-Chia Chen, [1,2,4]Chien-Tai Hong, [1,2,5]Nai-Fang Chi, [1,2,4]Chaur-Jong Hu, [1,2,4]Han-Hwa Hu, [1,2,4]Lung Chan, [3]Hung-Wen Chiu

[1]Department of Neurology, Shuang Ho Hospital, Taipei Medical University; [2]Department of Neurology, School of Medicine, College of Medicine, Taipei Medical University; [3]Graduate Institute of Biomedical Informatics, College of Medical Science and Technology, Taipei Medical University, Taipei; [4]Taipei Neuroscience Institute, Taipei Medical University; [5]Faculty of Medicine, School of Medicine, National Yang-Ming University, Taiwan

Abstract

Background: The risk and benefit of tissue plasminogen activator (tPA) for aged>80 years with acute ischemic stroke (AIS) are controversial. In this study, we investigated the safety and efficacy of tPA in this population and utilized the artificial neural network (ANN) to established outcome predictive models. *Methods:* We retrospectively reviewed the stroke registry data of patients with AIS, aged >80 years who arrived at the hospital within 3 hours from the onset of symptoms. The characteristics and the outcomes, presented as modified Rankin Scale (mRS), and mortality rate at 3 months between the tPA-treated and non-tPA groups were analyzed. An ANN algorithm was applied to establish predictive models. *Results:* A total of 80 patients aged>80 years with AIS were identified, and 49 of them received tPA. After adequate training, our ANN models accurately predicted the outcomes with the area under the receiver operating characteristic curves of 0.974, and a low error to predict the mRS score at 3 months. After applying our prediction model to those in the non-tPA group, we demonstrated the potential benefits in those patients if they had undergone tPA therapy.
Conclusions: Our results show that ANN can be a potentially useful tool for predicting the treatment outcomes of tPA. Such novel machine learning-based models may help with therapeutic decision making in clinical settings.

Keywords: artificial neural network, ischemic stroke, old age, outcome, prediction, thrombolysis

INTRODUCTION

Stroke is the second leading cause of death globally and the third leading cause of premature death and disability.[1,2] Consequently, stroke has a wide-ranging negative physical and economic impact on patients and their families.[1,2] Ischemic stroke accounts for 80% of total stroke.[3] Aging is negatively associated with recovery from and outcome of acute ischemic stroke (AIS).[4]

Currently, application of recombinant tissue plasminogen activator (tPA) is the most accessible and effective treatment for AIS. Since the 1990s, the inclusion and exclusion criteria have been revised several times following confirmation of the efficacy and safety of tPA in recent studies.[5] Nevertheless, the decision to waive age limitations for tPA among older adults aged >80 years was based only on clinical trials with small sample sizes. Furthermore, the findings of such studies in terms of the safety and efficacy of tPA among older adults were inconclusive. In practice, the use of tPA among older adults with AIS is not uncommon, but biased comparisons between tPA and non-tPA groups that lacked controls or did not use identical stroke management techniques have made it difficult for retrospective studies to confirm the safety and efficacy of tPA through conventional analysis.

Artificial intelligence (AI)-based techniques have quickly risen to prominence in health-related fields, and such techniques have been shown to be capable of assisting medical staff in disease diagnosis and prediction.[6] Supervised machine-learning methods can learn complex structures by using a training data set and apply that knowledge to predict the outcome of an

Address correspondence to: Hung-Wen Chiu, Professor, Graduate Institute of Biomedical Informatics, Taipei Medical University, 250 Wu-Hsing Street, Taipei, Taiwan. Tel: +886-2-66382736 ext.1511, E-mail: hwchiu@tmu.edu.tw

unobserved situation.[7] Artificial neural networks (ANNs) are a form of supervised machine learning. Such networks simulate the structure and functionality of biological neural systems, gathering knowledge by detecting patterns and relationships among data and learning through experience.[8] The most commonly applied ANN has a multilayer design, including an input layer, hidden layer, and output layer, with each layer consisting of many neurons. Each neural unit is connected with many others, and these links can be enforcing or inhibitory in their effect on the activation state of connected neurons. ANN-based models can effectively predict the complex nonlinear relationship between input and output variables by repeating the learning and validation process until a desirable regression is achieved.[9]

In this study, we aimed to (1) determine the safety and efficacy of tPA and identify factors associated with the outcomes of tPA use and (2) establish reliable outcome prediction models for patients aged >80 years through the use of ANNs.

METHODS

Participants

Medical records from the stroke registry of Shuang Ho Hospital in Taiwan were retrospectively reviewed for the period between January 2013 and December 2016. Data of patients who arrived at the emergency room (ER) with a suspected acute stroke within 3 hours from the onset of symptoms were obtained. All patients received noncontrast head computed tomography (CT) or brain magnetic resonance imaging (MRI). Inclusion criteria were as follows: patients with AIS, aged >80 years, and treated with tPA. The age-matched controls included patients with AIS who arrived at the ER within 3 h from the onset of symptoms, and those who had not been treated with tPA. Exclusion criteria were intracranial hemorrhage, an initial National Institute Health Stroke Scale (NIHSS) score of <6, and receiving surgical or intra-arterial intervention for AIS. Patients who received tPA treatment followed the American Heart Association/American Stroke Association (AHA/ASA) guidelines.[5,10] For patients who received tPA, a repeat brain image (CT or MRI) was performed at 24 hours to confirm AIS and to search for intracranial hemorrhage (ICH). For the non-tPA age-matched controls, a repeated brain image was performed between 24 to 72 hours after admission.

Following data were collected from patients' medical records: age, sex, history of hypertension, history of type 2 diabetes mellitus (T2DM), atrial fibrillation (AF), previous stroke, onset-to-hospital time, treated with or without tPA, and poststroke symptomatic ICH. Symptomatic ICH was defined as blood at any site in the brain, observed on the CT scan with the presence of clinical deterioration, documented by the investigator; or the occurrence of adverse events indicating clinical worsening related to symptomatic ICH.[11] All CT/MRI results were analyzed by two independent neurologists.

Moderate to severe stroke was defined as an NIHSS score ≥10.[12] Outcome parameters included modified Rankin Scale (mRS) score, mortality at 3 months, and presence of symptomatic ICH. A favorable outcome was defined as an mRS score ≤ 2, and a poor outcome was defined as an mRS score ≥ 3 at 3 months.[13-16]

Statistical analyses

All statistical analyses were performed using the JMP, version 11.0.0 software (SAS Institute Inc., Cary, NC, USA). Continuous variables are presented as means ± standard deviations, and categorical variables are expressed as numbers and percentages with their corresponding 95% confidence intervals (CI). One-way ANOVA was used for continuous variables, and Fisher's exact test was used for categorical variables. A correlation matrix was used to determine the associations among multiple variables and with the outcomes (i.e., age, sex, hypertension, T2DM, AF, previous stroke, treated with tPA or not, onset-to-hospital time, and initial NIHSS score). The variables where $p < 0.1$ were included into the multivariate logistic regression model to determine the independent predictors of stroke outcomes at 3-month follow-up. A p-value< 0.05 was considered statistically significant.

Application of ANN

To predict the outcomes for older adults with AIS, we developed two predictive ANN models by using the clinical features of patients as inputs. Both models contained the following input variables: patients' age, sex, history of hypertension, history of T2DM, AF status, history of previous stroke, initial NIHSS score, onset-to-hospital time, and whether tPA was received. Model 1 was designed to predict if each patient would have a favorable or poor outcome after stroke. Model 2 was designed to predict the mRS score at 3 months. Both ANN models were designed using STATISTICA version 10.0 (StatSoft, Tulsa, OK, USA). The applied architecture was a multilayer perceptron (MLP)

combined with a backpropagation algorithm. The number of perceptrons in the hidden layer was set empirically. A favorable or poor outcome (for Model 1) and the corresponding mRS score (for Model 2) were used as the targets of ANN models. Cross validation was conducted with an 80% training group and a 20% testing group. After appropriate training, the ANN selected the network structure with the most satisfactory performance. The area under the receiver operating characteristic curve (AUC) represented the performance of the ANN model 1. For Model 2, we recorded the correlation efficiency (r^2) as the performance of the model and reported the mean square error (MSE) for both training and testing subsets.

RESULTS

Clinical outcomes after thrombolytic therapy

Between 2013 and 2016, a total of 80 patients (52 women and 28 men) aged >80 years who experienced an acute stroke arrived at the ER within 3 hours from the onset of symptoms. The mean age of the patients was 84.4±3.5 years, and the mean initial NIHSS score was 17.5±7.5. Among them, 49 patients (61.2%) received intravenous tPA (0.6 mg/kg body weight). The mean door to needle time for those receiving tPA was 65.7±23.4 minutes. At baseline, the tPA and non-tPA groups had similar age and sex profiles. The tPA-treated group had a higher prevalence of previous stroke (p=0.005) and relatively milder initial symptoms than did the non-tPA group (Table 1). After follow-up for 3 months, the tPA-treated group had lower mRS scores than did the non-tPA group (p=0.007, Figure 1). In total, 39 patients in the tPA-treated group and 26 patients in the non-tPA group had initial NIHSS scores ≥10, indicating a moderate to severe stroke. For these patients, those treated with tPA also had a lower mortality rate (p=0.04) and a higher chance of a favorable outcome at 3 months (p = 0.036).

The incidence of ICH did not differ between the tPA-treated and non-tPA patients. Symptomatic ICH of any type occurred in 8.2% of the tPA-treated patients and 3.2% of the non-tPA treated patients (p=0.374).

Of the current cohort, 15 patients with a mRS score ≤2 at 3 months were defined as the favorable outcome group, and 65 patients with a mRS score ≥3 were defined as the poor outcome group (Table 2). There were no differences between age, sex, or the prevalence of previous medical conditions between these two groups. The poor outcome group had higher NIHSS scores at the

Table 1: Baseline characteristics of the patients aged > 80 years treated with and without tPA

	Treated without tPA	Treated with tPA	*P*-value
n	31	49	
Age (years)	85.2 ± 4.0	83.9 ± 3.1	0.135
Female, n (%)	22 (70.1)	30 (61.2)	0.373
Hypertension, n (%)	23 (74.2)	41 (83.7)	0.302
T2DM, n (%)	11 (35.5)	12 (24.5)	0.290
AF, n (%)	20 (64.5)	22 (44.9)	0.087
Previous stroke, n (%)	6 (19.4)	25 (51.0)	0.005*
Onset-to-hospital time (min)	68.5 ± 42.1	121.2 ± 40.2	<0.0001*
Door-to-needle time (min)		65.7 ± 23.4	
Initial NIHSS score	20.3 ± 8.1	15.8 ± 6.7	0.012*
Outcome measures			
mRS at 3 months	4.9 ± 1.4	3.8 ± 1.8	0.007*
ICH, n (%)	1 (3.2)	4 (8.2)	0.374
Mortality, n (%)	13 (41.9)	10 (20.4)	0.040*

Continuous variables are presented as means ± SD. One-way analysis of variance was used for continuous variables, and Fisher's exact test was used for categorical variables. AF - atrial fibrillation; ICH - intracranial hemorrhage. mRS - modified Rankin Scale; NIHSS - National Institutes of Health Stroke Scale; T2DM - type-2 diabetes mellitus; tPA - tissue plasminogen activator. *p-value<0.05

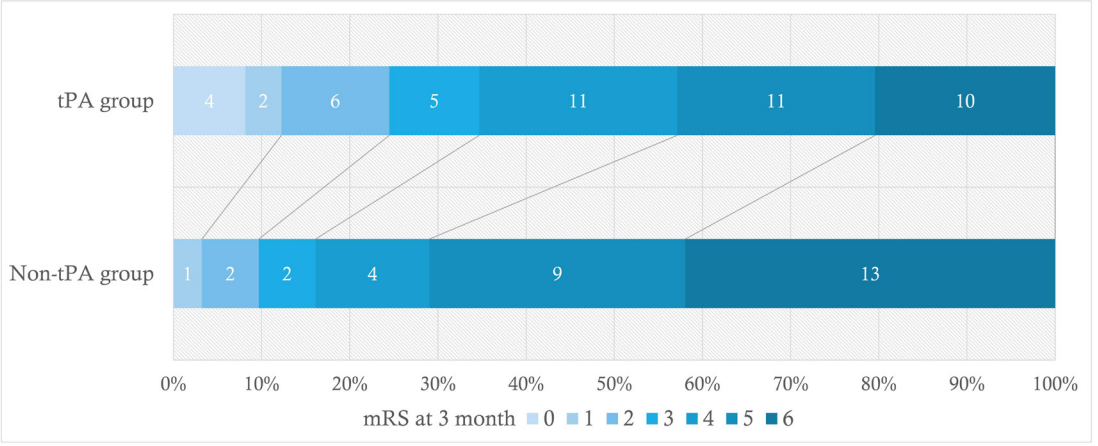

Figure 1. Functional outcomes of patients aged > 80 years with and without tPA treatment. The number in the bar indicates the number of patients. The tPA-treated group had a lower mRS score at 3 months when compared to the non-tPA group, p=0.007). mRS - modified Rankin Scale; tPA - tissue plasminogen activator.

ER (p<0.0001) and shorter onset-to-hospital times (p=0.037). In the entire cohort, the mRS score at 3 months was associated with initial NIHSS score (p<0.0001) and onset-to-hospital time (P=0.003).

A multivariate logistic regression model was applied to adjust the baseline variables with p values <0.1 in Table 2 to determine the following independent predictors of stroke outcomes: sex, treatment with tPA, onset-to-hospital time, and initial NIHSS score. Table 3 presents the crude and adjusted OR values of the variables in the logistic regression model. After adjusting for the associated variables, there was no difference between treatment with tPA and the outcome at 3 months. In the entire cohort, the outcome at 3 months was associated with initial NIHSS score (adjusted OR = 0.78; 95% CI: 0.67–0.91).

Table 2: Comparison of clinical variables between patients with favorable and poor outcomes

	Favorable outcome	Poor outcome	*p*-value	OR (95% CI)
n	15	65		
Age (years), OR: per year increase	83.9 ± 4.1	84.5 ± 3.4	0.497	1.05 (0.90-1.26)
Female, n (%)	7 (46.7)	45 (69.2)	0.099*	0.39 (0.12-1.22)
Hypertension, n (%)	13 (86.7)	51 (78.5)	0.474	1.78 (0.36-8.85)
T2DM, n (%)	3 (20.0)	20 (30.8)	0.406	0.56 (0.14-2.21)
AF, n (%)	7 (46.7)	35 (53.9)	0.616	0.75 (0.24-2.31)
Previous stroke, n (%)	7 (46.7)	24 (36.9)	0.485	1.49 (0.48-4.64)
Treated with tPA, n (%)	12 (80.0)	37 (56.9)	0.09*	3.03 (0.78-11.76)
Onset-to-hospital time (min), OR: per minute increase	123.9 ± 44.2	95.4 ± 47.8	0.037*	1.01 (1.00-1.03)
Initial NIHSS score, OR: per point increase	10.1 ± 4.0	19.2 ± 7.1	<0.0001*	0.78 (0.68-0.90)

Continuous variables are presented as means ± SD. p-value = between-group comparison. One-way analysis of variance was used for continuous variables, and Fisher's exact test was used for categorical variables. Favorable outcome was defined as mRS score ≤ 2 at 3 months. Poor outcome was defined as mRS score ≥ 3 at 3 months. AF - atrial fibrillation; CI, confidence intervals; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; tPA, tissue plasminogen activator; T2DM, type-2 diabetes mellitus; *p-value<0.1 and the variable was included into the regression model.

Table 3: Crude and adjusted OR for the 3-month favorable and poor outcomes for aged>80 years after tPA on a logistic regression model

Variables	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex (Female vs. Male)	0.39 (0.12-1.22)	0.71 (0.17-2.92)
tPA (with vs. without)	3.03 (0.78-11.76)	1.61 (0.25-10.52)
Onset-to-hospital time, per minute increase	1.01 (1.00-1.03)	1.01 (0.99-1.03)
Initial NIHSS score, per point increase	0.78 (0.68-0.90)	0.78 (0.67-0.91)

Favorable outcome was defined as mRS score ≤ 2 at 3 months. Poor outcome was defined as mRS score ≥ 3 at 3 months. CI, confidence intervals. mRS - modified Rankin Scale; NIHSS - National Institutes of Health Stroke Scale; OR, odds ratio; tPA - tissue plasminogen activator.

ANN Model 1

For Model 1, the ANN was trained to predict if patients would have a favorable or poor outcome at 3 months following AIS. After adequate training, the ANN model that contained 23 hidden perceptrons (MLP 15-23-2) had the most accurate performance, with training performance of 0.875 and testing performance of 0.938. The precision of the testing set was 100%, sensitivity was 66.67%, and the specificity was 87.5%. The AUC was 0.958 for the training set (Figure 2A) and 0.974 for the testing set (Figure 2B).

ANN Model 2

For Model 2, the ANN was trained to predict the mRS score at 3 months. After adequate training, the most accurate prediction model created with MLP was 15-4-1. The training performance was 0.812 (Figure 2C), and testing performance was 0.877 (Figure 2D). The MSE of the training set

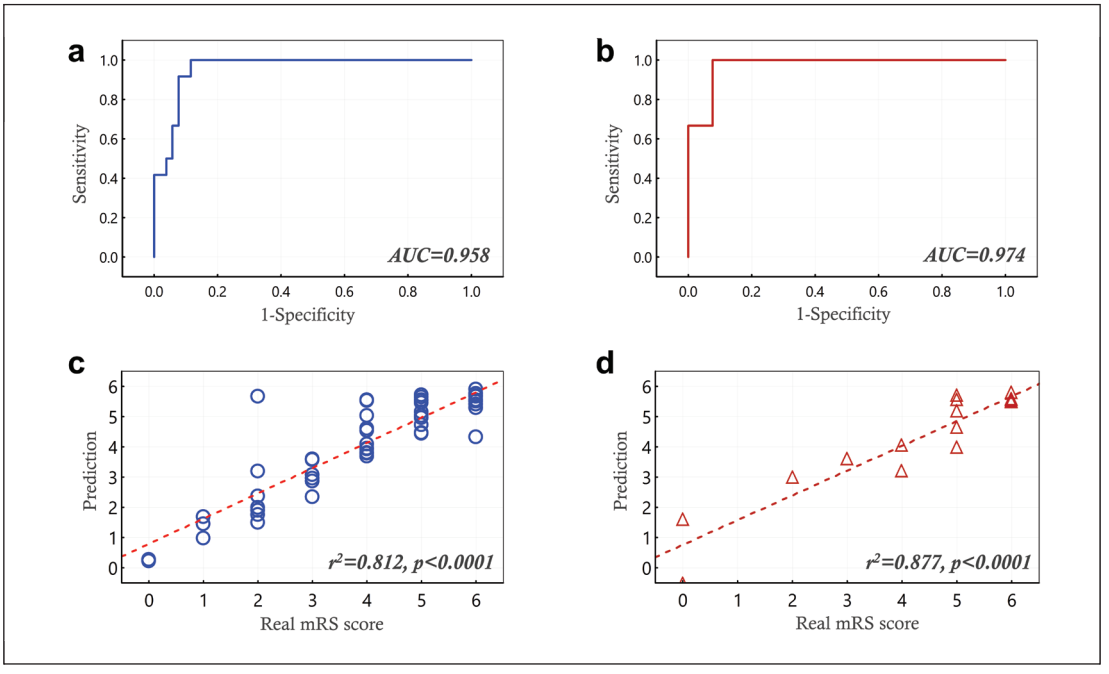

Figure 2. Performance of the ANN models.
The receiver operating characteristic (ROC) curves of Model 1 for predicting the patient outcomes. The blue line represents the training group (A) and the red line represents the testing group (B). AUC- area under the curve of ROC.
The performance of Model 2 for predicting the mRS score at 3 months. The X axis represents the real mRS score at 3 months and the Y axis represents the prediction. The blue circles indicate the training group (C) and the red triangles indicate the testing group (D). Best fit - red dashed lines. mRS - modified Rankin Scale.

was 0.26, and the MSE for the testing set was 0.24. The testing error was low, suggesting that the models both achieved reasonable predictive performance.

In the next step, we applied our ANN model to the non-tPA patients (n = 31) to determine their outcomes if they had been treated with tPA. We input the clinical information of the non-tPA group into Model 2 and obtained estimated post-tPA 3-month mRS scores, which reflected the patients' functional outcomes after stroke as if they had been treated with tPA at the acute stage. The results revealed that their estimated mean 3-month mRS score was 4.18±1.56, which was significantly lower than their actual mean 3-month mRS score of 4.84±1.39 (one-tailed matched pairs test, P=0.025, Figure 3). This indicated the benefit of tPA use among old adults with AIS aged >80 years.

DISCUSSION

This study established high-accuracy, ANN-based models to predict outcomes in older adults (age>80 years) with AIS. After training the ANN models, our Model 1 for predicting AIS outcomes achieved an accuracy with an AUC of 0.974 for the testing set. Model 2 for predicting the mRS score at 3 months also obtained a high accuracy with a low error (MSE=0.24) for the testing set. Through conventional analysis, our study initially found the functional outcomes of AIS to be associated only with the severity of stroke (Table 3). After applying the ANN prediction model to those in the non-tPA group, we demonstrated potentially beneficial outcomes in those patients if they had undergone tPA therapy.

Age is a crucial factor for the outcome of AIS.[17] People aged >80 years usually present with more severe AIS than their younger counterparts.[18] However, the application of tPA was originally prohibited among people of this age, which was mirrored in the inclusion criteria of the first large scale clinical trials of tPA in AIS.[19] The longer life expectancies and better healthy statuses of older adults challenged this artificial boundary. Subsequently, several studies claimed that the safety of tPA among older adults was no worse than that among younger populations.[20-23] However, a lack of age-matched controls in these studies was a major drawback of such comparison.[13,18,21,24,25] Moreover, comparisons between tPA and non-tPA groups with AIS in such studies were biased by nonidentical stroke management criteria, especially the time between stroke onset to first medical intervention. By contrast, the present study used age-matched controls with AIS who presented to the ER without the application of intravenous tPA. Our findings revealed no increase in symptomatic ICH events for any patient aged >80 years with AIS treated with tPA. In our

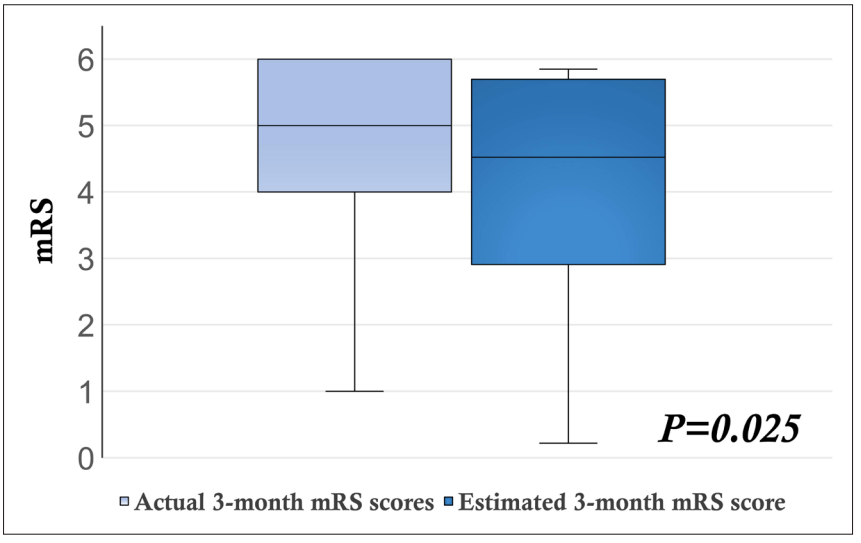

Figure 3. Comparison between the actual and estimated mRS scores of the non-tPA group.
The estimated score represented the predictive 3-month mRS score by ANN Model 2 for the non-tPA group as if they had been treated with tPA. The error bars represent the standard deviation of the mRS scores. ANN – artificial neural network. mRS - modified Rankin Scale; tPA - tissue plasminogen activator.Table 1. Baseline characteristics of the patients aged > 80 years treated with and without tPA.

cohort, the tPA-treated group had lower mRS scores than did the non-tPA group after follow-up for 3 months; however, significant differences arose from their baseline stroke severity. This is corroborated by findings indicating that age and initial NIHSS scores are critical predictors of stroke outcomes.[16,26] In the current cohort, our patients received a lower dose of tPA (0.6 mg/kg). While current AHA/ASA guidelines recommend an tPA dose of 0.9 mg/kg[5], during our study period between 2013 and 2016, thrombolysis for patients aged >80 years was still considered to be "off-label use"; experts have not achieved consensus regarding the standard dose in this age group.[10] Evidence from previous studies have proven the safety and efficacy of intravenous tPA of 0.6 mg/kg within 3 h of stroke onset, even for older patients aged >80 years; however, a recent open-label, randomized trial did not reveal a lower dose of tPA be equivalent to the standard dose with respect to death and disability at 90 days in AIS.[16,27-29] Thus, the "aging" and "tPA dose" effects may partially explain the fact that in our cohort, the regression model failed to demonstrate a beneficial response to tPA treatment in the older population.

To provide an early prognosis and identify patients with a high likelihood of poor outcomes from AIS despite intravenous tPA, a reliable tool for prediction of long-term AIS outcome is crucial. Accurate prediction can influence the decision-making process and lead to rapid, appropriate arrangements for invasive add-on treatment strategies such as endovascular intervention.[30] Several efforts have been made to create a clinical scoring system that can predict a patient's functional outcome of AIS, such as the Acute Stroke Registry and Analysis of Lausanne (ASTRAL)[31], the DRAGON[30] and the Totaled Health Risks in Vascular Events (THRIVE)[32] scores. Studies that have attempted to predict outcomes after intravenous thrombolysis based on clinical scoring items demonstrated acceptable predictive performance, with AUCs of approximately 0.7–0.9.[30,31,33,34] However, further improvement of predictive precision is warranted for clinical application. To date, no predictive tool has specifically focused on older adults aged>80 years.

Artificial intelligence techniques have rapidly gained prominence in health-related fields. Such techniques can enable investigation of nonlinear data relationships, enhance data interpretation, and lead to more efficient diagnostic and predictive methods. With the rapid development in modern computational technology and the progress in bioinformatics methodology, artificial intelligence-assisted diagnosis and medical supporting systems have changed and will continue to change medical practice. Stroke is a multi-factorial condition that causes damage to the central nervous systems. Developing a novel method with the assistance of artificial intelligence techniques can facilitate diagnosis and predict the outcome of acute stroke to enable early detection and treatment of this disease.

ANNs are a form of machine learning that can be used to create artificial intelligence. Such networks resemble the brain in two respects: 1) knowledge is acquired by the network from its environment through a learning process and 2) interneuron connection strengths, known as synaptic weights, are used to store the acquired knowledge [35]. Neural networks have many advantages, including requiring less input from the user and less formal statistical training, the ability to implicitly detect complex nonlinear relationships between dependent and independent variables, and the ability to detect all possible interactions between predictor variables.[7,35]

A supervised-learning ANN can emulate human expert diagnostic performance and identify relevant predictive markers in a diagnostic task.[9] One study that used ANN techniques found that an ANN could successfully differentiate between people with stroke and healthy controls by recognition of symptoms.[7] Recent studies have also shown the power of ANN to predict AIS after carotid artery stenting and to predict intracerebral hemorrhage and outcomes following thrombolytic therapy for acute AIS.[36-38] To our knowledge, this is the first study to use ANN for stroke outcome prediction among older adults. Our results revealed precise predictions, showing that ANNs can be effective tools for predicting the outcomes of tPA treatment with high accuracy. Through inputting simple variables, we could immediately predict the outcomes and estimate 3-month mRS scores with or without tPA therapy among elderly patients at admission. This information can have crucial clinical applications in the decision-making process for elderly patients with AIS.

The strength of our study is the use of a machine learning-assisted method focusing for older adults with AIS. Adequate and reliable outcome predictions can support the clinical decision-making process and direct future therapeutic plans. Our study demonstrated that, in older adults with AIS, an ANN can accurately predict prognosis through training with simple variables.

The resulting AUC can range up to 0.974, and the mRS score prediction demonstrated a low testing error. These findings have clinical significance as they prove that ANN-based predictive methods can be potential applied to the treatment of AIS.

One limitation of the present study was potential selection bias as well as lack of randomization between the tPA and non-tPA groups. Because the use of tPA to treat older adults is not reimbursed by Taiwan's National Health Insurance system, such a prescription is only possible if patients or their families are willing to pay themselves. Consequently, their baseline socioeconomic status, other health-related conditions, and severity of stroke can affect their decision to pursue treatment. Another selection bias is our study excluded the patients who received surgical or intra-arterial intervention followed by tPA. This might exclude the patients who had a poor outcome with intravenous tPA. Our study also had a small sample size as well as monocentric information; thus, additional multicenter studies with larger sample sizes are warranted to verify the results and develop models for those who undergo different treatment strategies for AIS. The other limitation was that from a traditional statistics viewpoint, the neural network is a non-identifiable model, and this might restrict the clinical interpretation of such models.

In conclusion, our study demonstrated that ANN techniques can be effectively used to accurately predict functional outcome in older adults with AIS. Furthermore, we demonstrated the novel machine learning-based models can be used to derive new knowledge and improve health care management. These results indicate that such models can be applied in clinical emergent settings with cases of AIS to help with therapeutic decision making.

DISCLOSURE

Ethics: The study protocol was approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB) (Approval No. N201705044).

Financial support: This study was partially funded by Taipei Medical University-Shuang Ho Hospital (Grant no. 100TMU-SHH-13)

Conflict of interest: None

REFERENCES

1. Chin JH, Vora N. The global burden of neurologic diseases. *Neurology* 2014;83(4):349-51.
2. Duncan PW, Zorowitz R, Bates B, *et al.* Management of adult stroke rehabilitation care: a clinical practice guideline. *Stroke* 2005;36(9):e100-43.
3. Ovbiagele B, Nguyen-Huynh MN. Stroke epidemiology: advancing our understanding of disease mechanism and therapy. *Neurotherapeutics* 2011;8(3):319-29.
4. Nichols-Larsen DS, Clark PC, Zeringue A, Greenspan A, Blanton S. Factors influencing stroke survivors' quality of life during subacute recovery. *Stroke* 2005;36(7):1480-4.
5. Furie KL, Jayaraman MV. 2018 Guidelines for the early management of patients with acute ischemic stroke. *Stroke* 2018;49(3):509-10.
6. Jiang F, Jiang Y, Zhi H, *et al*. Artificial intelligence in healthcare: past, present and future. *Stroke Vasc Neurol* 2017;2(4):230-43.
7. Abedi V, Goyal N, Tsivgoulis G, *et al*. Novel screening tool for stroke using artificial neural network. *Stroke* 2017;48(6):1678-81.
8. Agatonovic-Kustrin S, Beresford R. Basic concepts of artificial neural network (ANN) modeling and its application in pharmaceutical research. *Journal of pharmaceutical and Biomedical Analysis* 2000;22(5):717-27.
9. Amato F, López A, Peña-Méndez EM, Vaňhara P, Hampl A, Havel J. Artificial neural networks in medical diagnosis. *Journal of Applied Biomedicine* 2013;11(2):47-58.
10. Jauch EC, Saver JL, Adams HP, Jr., e*t al*. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke* 2013;44(3):870-947.
11. Hacke W, Kaste M, Fieschi C, *et al.* Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet* 1998;352(9136):1245-51.
12. Mihindu E, Mohammed A, Smith T, Brinster C, Sternbergh WC, 3rd, Bazan HA. Patients with moderate to severe strokes (NIHSS score >10) undergoing urgent carotid interventions within 48 hours have worse functional outcomes. *J Vasc Surg* 2019;69(5):1471-81.
13. Boulouis G, Dumont F, Cordonnier C, Bodenant M, Leys D, Henon H. Intravenous thrombolysis for acute cerebral ischaemia in old stroke patients >/= 80 years of age. *J Neurol* 2012;259(7):1461-7.
14. Mouradian MS, Senthilselvan A, Jickling G, *et al*. Intravenous rt-PA for acute stroke: comparing its effectiveness in younger and older patients. *J Neurol Neurosurg Psychiatry* 2005;76(9):1234-7.
15. Gomez-Choco M, Obach V, Urra X, *et al.* The response to IV rt-PA in very old stroke patients. *Eur J Neurol* 2008;15(3):253-6.
16. Kono S, Deguchi K, Morimoto N, *et al.* Intravenous thrombolysis with neuroprotective therapy by

edaravone for ischemic stroke patients older than 80 years of age. *J Stroke Cerebrovasc Dis* 2013;22(7):1175-83.
17. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009;8(4):355-69.
18. Bentsen L, Christensen L, Christensen A, Christensen H. Outcome and risk factors presented in old patients above 80 years of age versus younger patients after ischemic stroke. *J Stroke Cerebrovasc Dis* 2014;23(7):1944-8.
19. Kepplinger J, Barlinn K, Deckert S, Scheibe M, Bodechtel U, Schmitt J. Safety and efficacy of thrombolysis in telestroke: A systematic review and meta-analysis. *Neurology* 2016;87(13):1344-51.
20. Tanne D, Gorman MJ, Bates VE, *et al*. Intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 80 years and older : the tPA stroke survey experience. *Stroke* 2000;31(2):370-5.
21. Meseguer E, Labreuche J, Olivot JM, *et al*. Determinants of outcome and safety of intravenous rt-PA therapy in the very old: a clinical registry study and systematic review. *Age Ageing* 2008;37(1):107-11.
22. Longstreth WT, Jr., Katz R, Tirschwell DL, Cushman M, Psaty BM. Intravenous tissue plasminogen activator and stroke in the elderly. *Am J Emerg Med* 2010;28(3):359-63.
23. Bhatnagar P, Sinha D, Parker RA, Guyler P, O'Brien A. Intravenous thrombolysis in acute ischaemic stroke: a systematic review and meta-analysis to aid decision making in patients over 80 years of age. *J Neurol Neurosurg Psychiatry* 2011;82(7):712-7.
24. Engelter ST, Bonati LH, Lyrer PA. Intravenous thrombolysis in stroke patients of > or = 80 versus < 80 years of age--a systematic review across cohort studies. *Age Ageing* 2006;35(6):572-80.
25. Ford GA, Ahmed N, Azevedo E, *et al.* Intravenous alteplase for stroke in those older than 80 years old. *Stroke* 2010;41(11):2568-74.
26. Mobius C, Blinzler C, Schwab S, Kohrmann M, Breuer L. Re-evaluation of the stroke prognostication using age and NIH Stroke Scale index (SPAN-100 index) in IVT patients - the-SPAN 100(65) index. *BMC Neurol* 2018;18(1):129.
27. Chao AC, Liu CK, Chen CH, *et al*. Different doses of recombinant tissue-type plasminogen activator for acute stroke in Chinese patients. *Stroke* 2014;45(8):2359-65.
28. Cheng JW, Zhang XJ, Cheng LS, *et al*. Low-dose tissue plasminogen activator in acute ischemic stroke: A systematic review and meta-analysis. *J Stroke Cerebrovasc Dis* 2018;27(2):381-90.
29. Anderson CS, Robinson T, Lindley RI, *et al*. Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke. *N Engl J Med* 2016;374(24):2313-23.
30. Strbian D, Meretoja A, Ahlhelm FJ, *et al*. Predicting outcome of IV thrombolysis-treated ischemic stroke patients: the DRAGON score. *Neurology* 2012;78(6):427-32.
31. Ntaios G, Faouzi M, Ferrari J, Lang W, Vemmos K, Michel P. An integer-based score to predict functional outcome in acute ischemic stroke: the ASTRAL score. *Neurology* 2012;78(24):1916-22.
32. Flint AC, Cullen SP, Faigeles BS, Rao VA. Predicting long-term outcome after endovascular stroke treatment: the totaled health risks in vascular events score. *AJNR* 2010;31(7):1192-6.
33. Molina CA, Alexandrov AV, Demchuk AM, Saqqur M, Uchino K, Alvarez-Sabin J. Improving the predictive accuracy of recanalization on stroke outcome in patients treated with tissue plasminogen activator. *Stroke* 2004;35(1):151-6.
34. Cooray C, Mazya M, Bottai M, *et al*. External Validation of the ASTRAL and DRAGON Scores for Prediction of Functional Outcome in Stroke. *Stroke* 2016;47(6):1493-9.
35. Manning T, Sleator RD, Walsh P. Biologically inspired intelligent decision making: a commentary on the use of artificial neural networks in bioinformatics. *Bioengineered* 2014;5(2):80-95.
36. Dharmasaroja P, Dharmasaroja PA. Prediction of intracerebral hemorrhage following thrombolytic therapy for acute ischemic stroke using multiple artificial neural networks. *Neurol Res* 2012;34(2):120-8.
37. Ichinose N, Hama S, Tsuji T, *et al*. Predicting ischemic stroke after carotid artery stenting based on proximal calcification and the jellyfish sign. *J Neurosurg* 2018;128(5):1280-8.
38. Chung CC, Hong CT, Huang YH, *et al.* Predicting major neurologic improvement and long-term outcome after thrombolysis using artificial neural networks. *J Neurol Sci* 2020;410:116667.