International Journal of General Medicine

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ORIGINAL RESEARCH

Prediction of Long-Term Poor Clinical Outcomes in Cerebral Venous Thrombosis Using Neural Networks Model: The BEAST Study

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Introduction: Risk prediction models are commonly performed with logistic regression analysis but are limited by skewed datasets. We utilised neural networks (NNs) model to identify independent predictors of poor outcomes in cerebral venous thrombosis (CVT) due to the limitations of logistic regression (LR) analysis with complex datasets.

Methods: We evaluated 1309 adult CVT patients from the prospective BEAST (Biorepository to Establish the Aetiology of Sinovenous Thrombosis) study. The area under the receiver operating characteristic (AUROC) curve confirmed the goodness-of-fit of prediction models. The normalised importance (NI) of the NNs determines the significance of independent predictors.

Results: The stepwise logistic regression model found thrombolysis (OR 32.1; 95% CI 3.6–287.0; *P*=0.002), craniotomy (OR 6.9; 95% CI 1.3–36.8; *P*=0.02), and cerebral haemorrhage (OR 4.5; 95% CI 1.3–15.4; *P*=0.01) as predictors of poor clinical outcome with the AUROC of 0.71. Conversely, the NNs model identified major independent predictors of long-term poor clinical outcomes as cerebral haemorrhage (NI 100%) and thrombolysis (NI 98%), as well as trivial predictors of age (NI 2.8%) and altered mental status (NI 3.5%). The accuracy of the NNs model was 95.1% and 94.1% for self-learned randomly selected training and testing samples with an AUROC of 0.82. Positive and negative predictive values for poor outcomes were 13.2% and 97.1% for the LR model, compared with the NNs model of 18.8% and 98.7%, respectively.

Conclusion: Cerebral haemorrhage and thrombolysis was a strong independent predictor, whereas age merely impacts the long-term poor clinical outcome in adult CVT. Integrating unorthodox neural networks risk prediction model can improve decision-making as it outperforms conventional logistic regression with complex datasets.

Keywords: cerebral venous thrombosis, neural network, stroke, predictors, outcome

Introduction

Cerebral venous thrombosis (CVT) is a relatively rare (0.5–1%) form of stroke,[1–3] which can cause a severe and permanent disability in 6–10% of cases with ~15% of patients requiring bed rest or hospital admission due to the recurrence of severe headaches.[4–10] Clinicians especially radiologists should be able to recognise CVT promptly, which would facilitate the administration of anticoagulation therapy to prevent the progression of the disease and notably decrease the likelihood of acute complications and long-term sequelae.[8] Although several small studies have documented the potential predictors of poor clinical outcomes,[11–15] in a real-world scenario, the rarity of CVT disease poses several challenges, such as dealing with a heterogeneous group of patients with phenotypic diversity, lack of (or missing) patient data often causing skewed distributions and nonlinear relationships with incomplete datasets.[16] Thus, analysis of such rare disease datasets can be limited by poor quality and heterogenicity, whereas advanced statistical approaches like multilayer mathematical algorithm-based neural networks potentially offer greater efficiency over regression models where the dependent variable requires a linear relationship with the regression parameters.[17]

Received: 12 March 2024
Accepted: 25 June 2024
Published: 2 July 2024

The neural networks perceptron is an advanced mathematical algorithm that mimics how biological neurons communicate within a network.[18,19] Unlike the logistic regression model, a multilayer neural networks (NNs) model has self-learning capabilities, nonlinear mapping and a high degree of fault tolerance, which can determine the association between a series of independent variables and the output (dependent) variables by training and testing the neural network.[18–20] The NNs model outcome is decisive in the presence of skewed and incomplete datasets, nonlinear relationships, and lack of significant β coefficient value in the logistic regression analysis, as exemplified in a study used to identify predictors of poor prognosis following acute ischemic stroke.[21] Furthermore, this multilayer NNs perceptron has been shown to achieve a better predictive performance compared to logistic regression to predict the risk of congenital heart disease, cancers, and the mortality risk of liver failure.[22–27]

To identify predictors of long-term poor clinical outcomes following CVT, we used the neural networks model on (the necessarily skewed) data from the BEAST (Biorepository to Establish the Aetiology of Sinovenous Thrombosis) study, an international multicentre prospective observational study on cerebral venous thrombosis.[28] We go on to compare and validate the results from the NNs model with a stepwise multivariate logistic regression analysis to predict long-term poor clinical outcomes following CVT.

Patients and Methods

The BEAST Study

The BEAST is an international prospective observational study whose protocol has been published in detail elsewhere.[28] Briefly, the study recruited adult CVT patients aged ≥18 years with detailed phenotypic data from eleven tertiary care centres located in Belgium, Finland, France, Greece, Italy, Mexico, Netherlands, Portugal, Sweden, United Kingdom, and the USA (white non-Hispanic) between 2000 and 2018. Diagnosis of CVT was confirmed by angiography, either conventional, computed tomography venography (CTV), magnetic resonance (MR) imaging or dedicated venography, as previously described.[28] Ethical clearance was granted from all participating institutions from local institutional review boards, and the study complies with the Declaration of Helsinki. Informed written consent was obtained for all patients, and data was encrypted. For the purpose of this study, 6-month follow-up was defined as long-term, and this was the endpoint evaluated for statistical analysis.

Study Variables

We analysed 21 potential independent variables based on the age of CVT onset, gender, the occurrence of clinical symptoms, brain imaging characteristics including CVT location, and acute-phase treatment modalities (heparin, endovascular thrombolysis and decompressive craniotomy).[1–5,11–13,29–31] Further, we purposefully inputted severe cases that required intervention, e.g. thrombolysis and craniotomy, into the feedforward multilayer neural networks perceptron, predicting it would successfully identify these high-risk groups. The modified Rankin scale (mRS) was assessed at a 6-month follow-up, and patients were classified as independent survivors (mRS score 0–2) or dependent/dead (mRS score 3–6) patients.[9] The primary study outcome was to identify the independent predictors of dependent/dead (mRS score 3–6) CVT patients by comparing the results using neural networks and the LR model.

Statistical Analysis

We utilised SPSS v25.0 statistical software for windows to conduct conventional logistic regression (LR) and an unorthodox multilayer neural networks (NNs) model to identify predictors of poor clinical outcomes in CVT. Initially, we used a univariate analysis based on gender distribution, utilising appropriate statistical tests and observing a 95% confidence interval (CI) and odds ratio (OR) to define the risk patterns in the dataset. We evaluated the predictive model's performance using multivariate stepwise logistic regression (LR) analysis cross-validated by multilayer neural networks (NNs) model in the presence of skewed, incomplete, and non-linear relationships of 21 independent variable datasets. The goodness-of-fit of the NNs and LR models was evaluated with the area under the receiver operating characteristic (AUROC) curve. Data quality assessment was performed with Little's Missing Completely At Random (MCAR) test. Multicollinearity, the strength of the correlation among independent variables, was also tested and expressed by the collinearity tolerance and the variance inflation factor (VIF) value, where VIF >10 or tolerance <0.1 indicated the presence of significant multicollinearity that required to be optimised; otherwise, potentially causing concerns for the regression model outcome.[17] The statistically significant threshold was set at a *P*-value <0.05.

Logistic Regression Model

Logistic regression is a parametric algorithm for binary and linear classification problems that accomplish outcomes by predicting the probability of a set of independent variables.[17] Logistic regression utilised the sigmoid logistic function for mapping the predictions and probabilities to a range between 0 and 1.[17,18] Although study variables can be selected through different techniques and methods, yielding various regression models, they generally work similarly. The stepwise logistic regression model is a combination of forward or backwards methods and is used to determine which variables to add to or drop from the model sequentially based on statistical criteria. The logistic regression model has a linear decision surface, and the regression coefficient, usually the odds ratio, describes the impacts of independent predictors on the outcome.[17–19]

Multilayer Neural Networks Model

Feedforward neural networks, a non-parametric method and multilayer perceptron,[18] use mathematical algorithms to simulate neuronal architectural networks structurally and functionally.[20,21] A perceptron might be a single or multilayer computational algorithm model composed of multiple biological neurons capable of training neurons and supervised learning of binary classifiers to draw a decision or output. We utilised a three-layer (input, hidden, and output) feedforward NNs perceptron for the measurements of independent predictors, as NNs generate an outcome by self-learning from a potential correlation between dependent and independent variables through the training and testing process.[18–21] The first (input) layer comprises 21 neurons into which all independent variables were entered into the NNs model following a normalisation process through a standard rescaling of the covariates. The second (hidden) layer comprises 8 neurons where the sigmoid activation function is utilised for the computational and differential weighing of the independent variables. Finally, the third (output) layer is two neurons where the outcome is generated via the softmax function based on the random selection of a valid sample for all variables by the self-learned neural networks perceptron using SPSS statistical software functions.[18,20] Although we tested both sigmoid and hyperbolic tangent activation functions, the sigmoid activation function was utilised for the hidden layer to predict the probability which exists between the range of "0 and 1", which is similar to the LR model. Further, utilisation of the softmax function for the output layer improves the multiclass classification. The NNs perceptron training was the batch type, and the optimisation algorithm was scaled conjugate gradient. The neural networks topology for independent variables with multi-layered perceptron is shown in Figure 1.

The neural networks model can justify the study outcome by linking predicted with factual values, minimising the error in predicting default, and does not restrict the input (specific distribution) variables.[18–24] This model was validated by the ROC (receiver operating characteristic) curve, which observed the goodness of fit for predicting the model for all possible cut-offs by a diagram of sensitivity versus specificity. The AUC (area under the curve) is based on the non-parametric Mann–Whitney *U*-test, used as the dimensional index, which measures the accuracy of the predictor models in predicting death or dependency. The normalised importance (NI) value[20,21,24–27] of independent variables is expressed as a percentage in the NNs model outcome graph; a higher NI value represents better predictive power and vice versa to determine the significance of independent predictors for death or dependency.

Results

Characteristics of the Study Population

The BEAST study included 1309 subjects (75.5% female). The overall median (IQR-Interquartile Range) age of CVT onset was 37 (28–47) and 46 (35–58) years for women and men, respectively (*P*<0.001). Table 1 describes the baseline characteristics study population, including presenting symptoms on admission, radiological findings, treatment options and mRS scale 3–6 at 6 months post-CVT onset. The VIF value of the multicollinearity test demonstrated no significant

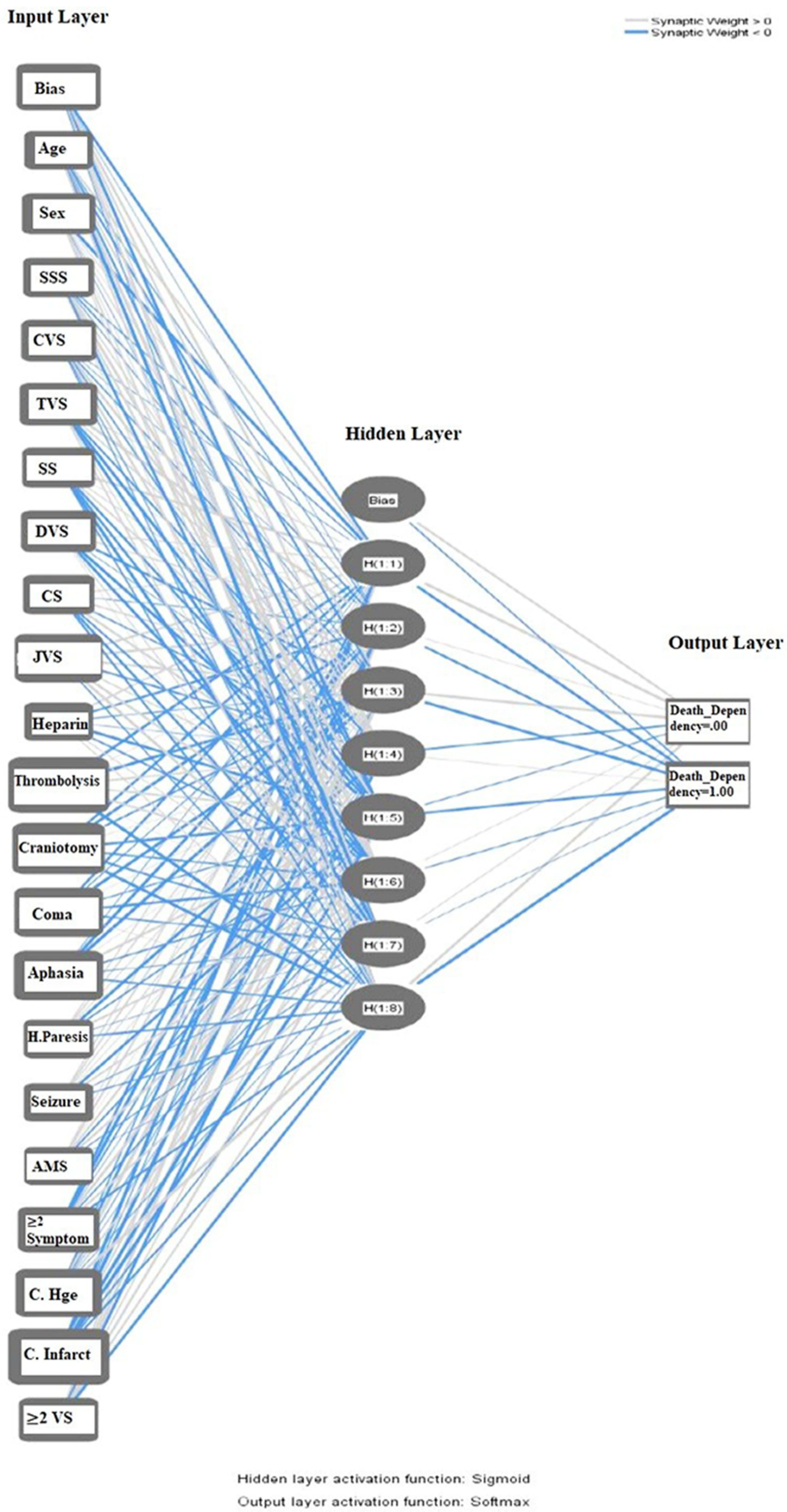

Figure 1 The neural networks topology with multi-layered perceptron. The figure illustrates twenty-one independent variables entering into the NNs model through the first layer neurons followed by computational weighing in the second (hidden) layer by sigmoid activation function. The output layer comprises two neurons that generate the model outcome using the softmax function. The grey and blue lines represent the synaptic weight, either >0 or <0, respectively. In addition to AUROC curve, this NNs model accuracy rate was 95.1% and 94.1% in training and testing phase.

Abbreviations: SSS, Superior sagittal sinus; CVS, Cortical venous sinus; TVS, Transverse venous sinus; SS, Straight sinus; DVS, Deep venous sinus; CS, Cavernous sinus; JVS, Jugular veins; H.Paresis, Hemiparesis; AMS, Altered mental status; C. Hge, Cerebral haemorrhage; C. Infarct, Cerebral Infarct; ≥2 VS, Venous sinus.

Table 1 Characteristics of Study Population

Variables	Sample (n/N) (%)	Women	Men	*P*-value	OR (95% CI)
Age (Median; IQR)	1309 (100%)	37 (28–47)	46 (35–58)	<0.001	-
Aphasia	116/619 (18.7%)	90 (14.5%)	26 (4.2%)	0.70	0.91 (0.56–1.47)
Hemiparesis	241/682 (35.3%)	188 (27.6%)	53 (7.8%)	0.59	0.90 (0.62–1.31)
Seizure	282/687 (41.0%)	228 (33.2%)	54 (7.8%)	0.07	0.71 (0.49–1.03)
Altered mental status	197/606 (32.5%)	149 (24.6%)	48 (7.9%)	0.80	1.10 (0.70–1.56)
≥2 presenting symptoms	127/535 (23.7%)	101 (18.9%)	26 (4.8%)	0.29	0.7 (0.5–1.3)
Coma (GCS ≤8)	53/596 (8.9%)	34 (5.7%)	19 (3.2%)	0.04	1.84 (1.01–3.35)
Cerebral infarction	208/591 (35.2%)	165 (27.9%)	43 (7.3%)	0.28	0.8 (0.5–1.2)
Cerebral haemorrhage	285/863 (33.0%)	225 (26.1%)	60 (6.9%)	0.23	0.8 (0.6–1.1)
Superior sagittal sinus	519/969 (53.6%)	391 (40.4%)	128 (13.2%)	0.57	1.1 (0.8–1.5)
Cortical veins	110/577 (19.1%)	82 (14.2%)	28 (4.9%)	0.63	1.1 (0.7–1.8)
Transverse sinus	399/870 (45.9%)	297 (34.1%)	102 (11.7%)	0.44	1.1 (0.8–1.5)
Straight Sinus	139/880 (15.8%)	109 (12.4%)	30 (3.4%)	0.45	0.8 (0.5–1.3)
Cavernous sinus	22/541 (4.1%)	18 (3.3%)	4 (0.7%)	0.61	0.7 (0.2–2.1)
Deep veins	64/558 (11.5%)	55 (9.9%)	9 (1.6%)	0.055	0.5 (0.2–1.0)
Jugular veins	228/635 (35.9%)	170 (26.8%)	58 (9.1%)	0.46	1.2 (0.8–1.7)
≥2 venous sinus	291/529 (55%)	217 (41.0%)	74 (14.0%)	0.46	1.2 (0.8–1.7)
Heparin	868/929 (93.4%)	677 (72.9%)	191 (20.6%)	0.09	0.6 (0.35–1.1)
Thrombolysis	36/561 (6.4%)	29 (5.2%)	7 (1.2%)	0.43	0.7 (0.3–1.7)
Surgical craniotomy	23/540 (4.3%)	17 (3.2%)	6 (1.1%)	0.8	1.1 (0.4–2.9)
Death or Dependency at 6 months	22/421 (5.2%)	15 (3.6%)	7 (1.7%)	0.12	2.1 (0.8–5.2)

Notes: n=positive case, N=Total available sample; P value reached from Chi Square test, Mann–Whitney *U*-test utilized for Median (IQR) value, and Fisher exact test when sample size <5.

correlation; the majority VIF was ≤2, except for multiple (≥2) sinus thrombosis and multiple (≥2) presenting symptoms where maximum VIF and collinearity tolerance were 3.2, 0.31, and 4.3, 0.23, respectively, among independent variables. Furthermore, the Little's Missing Completely At Random (MCAR) test also observed a *P*-value of 0.75, Chi-squared =0.09, indicating our data are randomly missing.

Multivariate Logistic Regression Model

The performance of the predicting model was initially tested with the stepwise logistic regression (LR) model for women and men separately (Table S1) as well as in combination (Table 2), which found statistically ambiguous Results with significantly high OR and wide confidence interval. Furthermore, the multivariable forward stepwise logistic regression model (Table 2) found that the following factors were potential independent predictors of poor clinical outcome at 6-month follow-up: endovascular thrombolysis (OR 32.1; 95% CI 3.6–287.0; *P*=0.002), craniotomy (OR 6.9; 95% CI 1.3–36.8; *P*=0.02), and cerebral haemorrhage (OR 4.5; 95% CI 1.3–15.4; *P*=0.01). The goodness-of-fit for the logistic regression model showed an AUROC curve of 0.71; 95% CI 0.56–0.85 (shown in Figure 2a). The sensitivity and

Table 2 Stepwise Multivariate Logistics Regression Analysis Observed Independent Predictors of Poor Clinical Outcome "Death or Dependency" in CVT

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
								Lower	Upper
Step 1[a]	Craniotomy	2.59	0.78	10.85	1	0.001	13.40	2.86	62.74
	Constant	−3.10	0.29	110.81	1	0.000	0.04	–	–
Step 2[b]	Thrombolysis	3.28	1.05	9.75	1	0.002	26.60	3.39	208.52
	Craniotomy	2.77	0.79	12.04	1	0.001	15.96	3.33	76.28
	Constant	−3.28	0.32	103.74	1	0.000	0.03	–	–
Step 3[c]	Thrombolysis	3.47	1.11	9.66	1	0.002	32.17	3.60	287.07
	Craniotomy	1.93	0.85	5.16	1	0.023	6.93	1.30	36.88
	Cerebral haemorrhage	1.52	0.62	6.04	1	0.014	4.59	1.36	15.47
	Constant	−3.82	0.45	69.83	1	0.000	0.02	–	–

Notes: Variable(s) entered on step 1. [a]Craniotomy; on step 2. [b]Thrombolysis; on step 3.[c]Cerebral haemorrhage.

specificity of the LR model were 58.82% and 78.15%, respectively, with a positive predictive value of 13.2% (95% CI 8.8–19.2%) and a negative predictive value of 97.1% (95% CI 95.0–98.4%) (Table 3).

Neural Networks Model

As the dataset was skewed and had a non-linear relationship, a non-parametric analysis using the multilayer NNs model was utilised to cross-validate the robustness of the results of the LR model. The neural networks model again evaluated

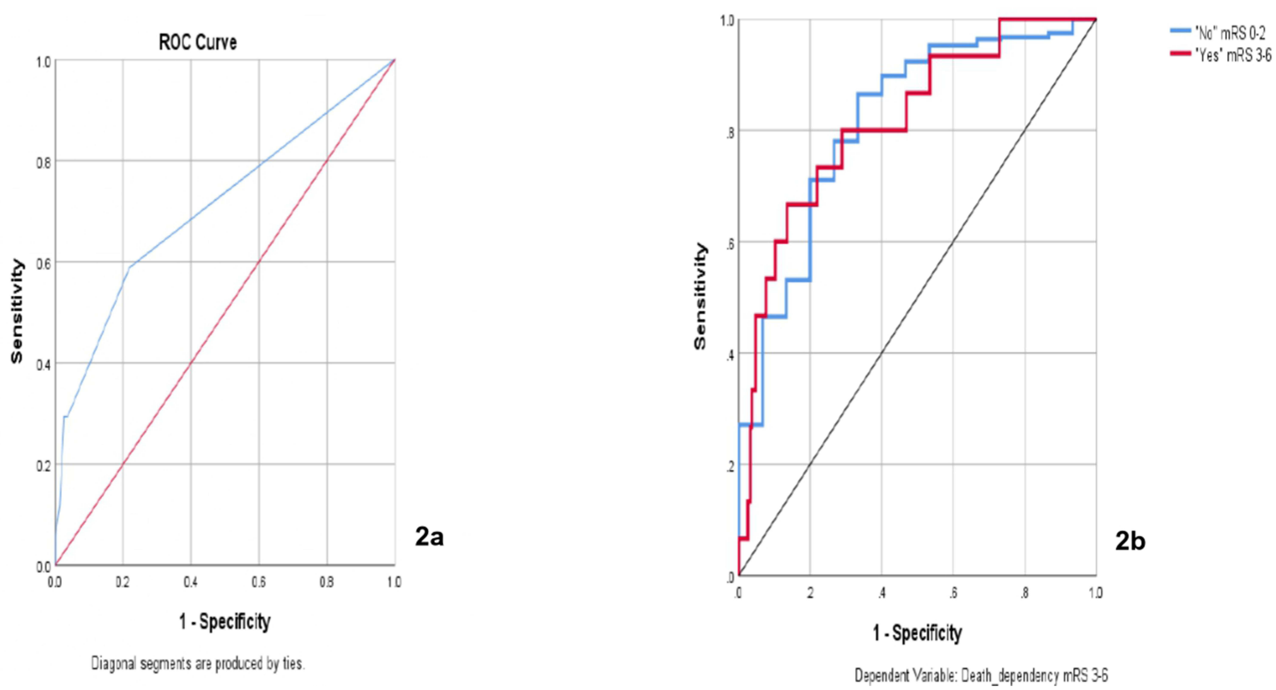

Figure 2 ROC curve measuring accuracy of the predicting model for death or dependency at 6-month; AUC for (**a**) logistics regression model 0.71 (AUC for women 0.76; 95% CI 0.58–0.93, and men 0.71; 95% CI 0.48–0.93), (**b**) NNs model 0.82 (red line).

Table 3 Comparison of the Goodness-of-Fit and Accuracy of the Neural Networks and Logistic Regression Risk Prediction Model

Performance Indices	Neural Networks Perceptron	Logistic Regression Model
Algorithms	Non-parametric method	Parametric method
Datasets	Skewed, non-linear and complex datasets.	Simple and linear datasets.
Activation function	Sigmoid logistic function	Sigmoid logistic function
Output (Independent predictors)		
Strong	Cerebral haemorrhage, thrombolysis, and craniotomy	Thrombolysis, craniotomy, cerebral haemorrhage
Trivial	Age, altered mental status	-
Self-learned model accuracy	95.1% in training and 94.1% in testing sample	-
Hosmer-Lemeshow statistics	-	0.71
Area under the ROC curve	0.82	0.71
Sensitivity	80.0%	58.8%
Specificity	81.0%	78.2%
Positive predictive value (PPV)	18.8%; 95% CI 13.9– 24.7%	13.2%; 95% CI 8.8–19.2%
Negative predictive value (NPV)	98.7%; 95% CI 96.3–99.5%	97.1%; 95% CI 95.0%-98.4%

all 21 independent study variables and the final output layer, where the model outcome is generated via the softmax function based on the random selection of a valid sample of 288 populations by the self-learned NNs model. Of these subjects, 70.5% and 29.5% of cases were utilised as training and testing samples to predict death or dependency, with an excellent accuracy level of 95.1% and 94.1%, respectively. Moreover, the ROC curve for the NNs model (shown in Figure 2b) showed the sensitivity and specificity for good and poor clinical outcomes constructed on the training and testing illustrations. The AUROC was 0.82 for predicting death or dependency, indicating the models' improved accuracy through a learning process.

The NI of independent variables by the NNs model to predict death or dependency at a 6-month follow-up shown in Figure 3. The NNs analysis determined that the most powerful predictors of death or dependence were cerebral haemorrhage (NI 100%), endovascular thrombolysis (NI 98%) and craniotomy (NI 73.8%). Conversely, age (NI 2.8%) altered mental status (NI 3.5%), heparin (NI 3.6%), and seizure (NI 5.0%) barely influenced the model. Furthermore, the sensitivity and specificity of the NNs model were 80.0% and 80.95%, respectively, with a positive predictive value of 18.8% (95% CI 13.9–24.7%) and a negative predictive value of 98.7% (95% CI 96.3–99.5%) (Table 3).

Discussion

Using data from a large prospective adult CVT cohort, we show that the feedforward multilayer NNs model effectively identifies either strong or trivial independent predictors of death or dependency, whereas stepwise LR analysis only demonstrated potential predictors. Our NNs model has an accuracy of 95.1% and 94.1% in the training and testing phase, respectively, to predict death or dependence with a better AUROC curve of 0.82, compared to the LR model AUROC curve of 0.71. Additionally, positive and negative predictive values for the NNs and LR model were 18.8% vs 13.2%, and 98.7% vs 97.1% predicting poor long-term clinical outcomes in CVT. In the presence of a wide confidence interval in the stepwise logistic regression model, independent predictors with high ORs and P<0.05 become ambiguous; hence we utilised feedforward neural networks, a non-parametric analysis to cross-validate the robustness of LR model findings.

Implementation and Interpretation

The ultimate goal of NN is to integrate multilayer neural networks perceptron into clinical practice to complement decision-making, particularly in complex datasets with missing data and non-linear relationships such as the BEAST data.[16,17]

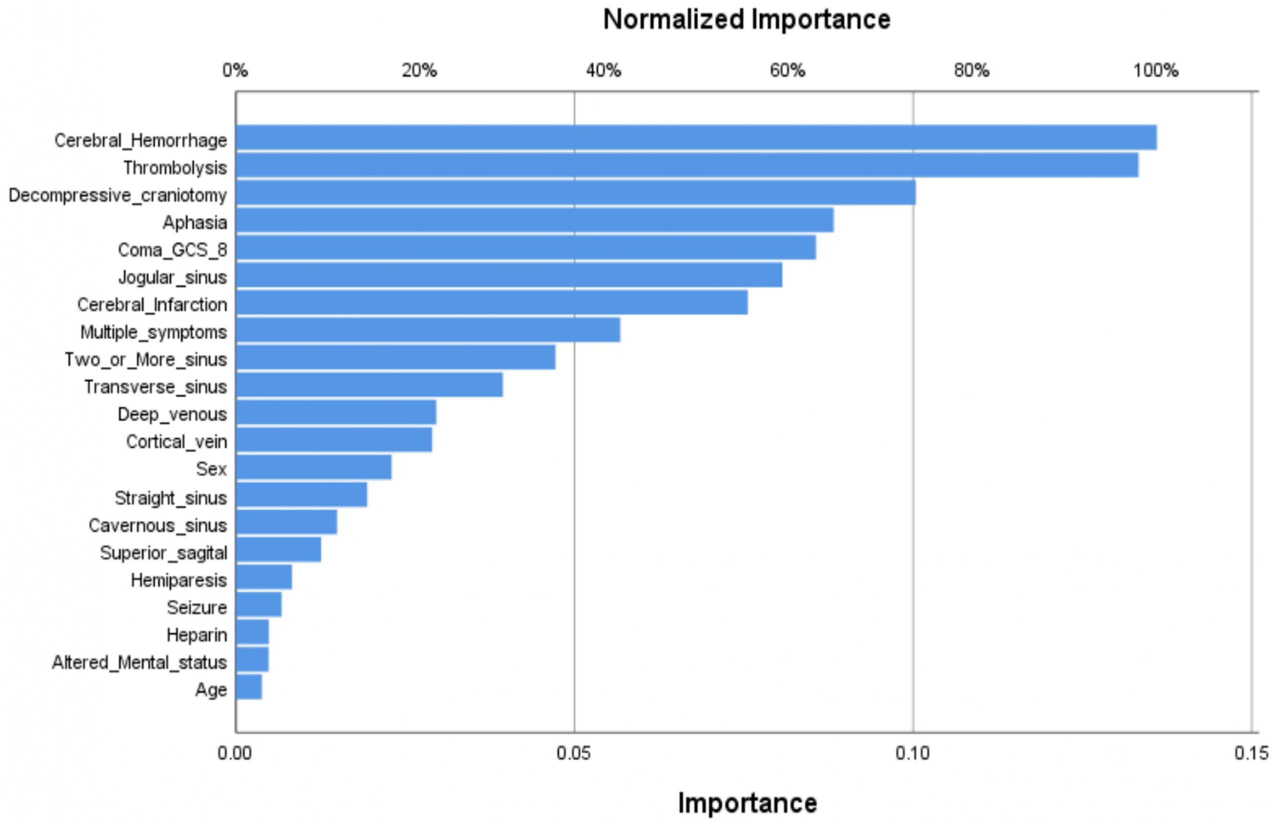

Figure 3 Normalised Importance (NI) of independent variables by the multilayer neural networks model. A greater NI percentage represents more powerful independent predictors and vice-versa for predicting death or dependency in CVT. Thus, cerebral haemorrhage (NI 100%) contributes decisively to the networks while age (NI 2.8%) barely.

A logistic regression model is comparatively easier to implement, interpret and require less computational work than neural networks. However, logistic regression models rely on assuming a linear relationship and the absence of extreme outliers in the dataset to log odds and express probabilities.[17,18] Unlike neural networks, logistic regression models generally include only statistically significant variables with a $P<0.05$ predicting an outcome. Further, neural networks outperform logistic regression in complex relationships due to data rarely being linearly separable in real-world situations.[18–20]

Generalisability and Capability

Unlike the LR model, a multilayer neural networks perceptron has a high degree of fault tolerance and better potential to determine the arbitrary association between independent and dependent variables, a result that supports our study findings.[18] Further, multilayer neural networks are a better fit over LR analysis (parametric test) for a skewed complex and non-linear dataset due to their non-parametric nature, which can identify all plausible interactions through the multiple training and testing algorithms between independent and dependent variables.[21–27]

Accuracy, Goodness-of-Fit, and Cross-Validation of the Models

Like current study results, an abnormally wide 95% CI and a more significant beta coefficient represent poor fitness of the regression model.[17] Conversely, the NNs model uses the AUROC curve with its training and testing sample accuracy report to confirm the goodness-of-fit based on a self-recruited random sample.[18–20] A better goodness-of-fit and higher accuracy of neural networks model were observed in several clinical studies with AUROC value; AUC 0.87,[22] AUC 0.77,[24] AUC 0.88,[32] and AUC 0.98.[33] Furthermore, previous studies also support our findings with better predictive performances of NNs than the LR model with a higher AUROC curve value of 0.88 vs 0.81,[21] 0.81 vs 0.74,[25] and 0.84 vs 0.76,[27] respectively. Nonetheless, a logistic regression model is less prone to overfitting than NNs because they involve simpler relationships between the outcome and predictor variables,[19–23] which is why NNs outperformed the LR model on the complex BEAST datasets.

Neural Networks and the BEAST Findings

Our NNs model finds that cerebral haemorrhage, endovascular thrombolysis, decompressive craniotomy, aphasia, and coma are independent predictors of death or dependency, confirmed by previous small studies and case series.[1,5,11,13,29–31] Furthermore, the recent randomised controlled TO-ACT trial[34] and a meta-analysis[35] observed that endovascular thrombectomy with or without thrombolysis is associated with poor functional outcomes and a higher mortality rate in CVT patients, which also supports the findings of our NNs model outcome.

Strength and Limitations

This is a large multinational prospective observational study on adult CVT patients, and the major strength is the robust collaboration and participation of multiple regional hospitals from different countries and reducing a potential source of recruitment bias. As data from the BEAST exclude those <18 years of age, our results do not apply to childhood CVT. The incompleteness of follow-up and the missing dataset is a possible source of bias; nonetheless, a quality control analysis observed no significant differences between missing and non-missing cases for each study variable. Although severe cases treated with thrombolysis and craniotomy might be a source of bias, the NNs used the mRS score assessed by stroke and neurology experts during a 6-month follow-up after CVT onset, which mitigates the risk of outcome bias. Despite the ability to determine statistical inferences of independent predictors with odds ratios, probability values, and confounding, constructing logistic regression models can be more challenging than NNs as it requires a strong understanding of statistical concepts. Although multilayer neural networks perceptron is a potential tool for analysing a non-linear complex relationship, the model is prone to overfit because of its speculative “Black Box” nature on the depth and complexity of the network and greater computational burden. Finally, the low positive and high negative predictive values might be a concern of outcome bias; however, considering the rare event of ‘dependent/death’ from an already rare disease of CVT with an excellent goodness-of-fit of the prediction models mitigates this potential bias.

Conclusion

Cerebral haemorrhage and thrombolysis are identified as potential independent predictors of long-term poor clinical outcomes in adult CVT. This unorthodox multilayer neural networks outperforms the conventional logistic regression model in risk prediction for complex datasets. Determining the best prediction model can be challenging as each model possesses unique advantages, and selection should consider these, along with datasets and study objectives.

Ethical Approval

Ethical clearance approval for this study was obtained from the London – Riverside Research Ethics Committee; REC reference: 04/Q0401/40.

Informed Consent

Written informed consent was obtained from all subjects prior to recruitment.

Acknowledgments

We utilized the Bio-Repository to Establish the Aetiology of Sinovenous Thrombosis (BEAST) datasets and are grateful to our patients for their participation and cooperation.

BEAST Collaborators

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by grants awarded to P.S. from the Stroke Association (UK) and the Dowager Countess Eleanor Peel Trust (UK). P.S. was funded by a Department of Health (UK) Senior Fellowship at Imperial College London for part of this study. The cohort of 231 French cases was constituted during a hospital protocol of clinical research approved by the French Ministry of Health; the biological collection was kept and managed by INSERM CIC-

CRB 1404, F-76000 Rouen, France. The controls from Belgium were genotyped as part of the SIGN study. R.L. is a senior clinical investigator of FWO Flanders. T.T. is the recipient of funding from the Sigrid Juselius Foundation (Finland), Helsinki University Central Hospital (Finland), Sahlgrenska University Hospital (Sweden), and the University of Gothenburg (Sweden). The Swedish Research Council (2018-02543) and the Swedish Heart and Lung Foundation (20190203) also supported the study. J.M.C. has received funding from the Dutch Thrombosis Foundation. This material results from work supported by resources and the use of facilities at the VA Maryland Health Care System, Baltimore, Maryland, and was also supported in part by the National Institutes of Health (U01NS069208, R01NS105150, and R01NS100178).

Disclosure

The authors report no conflicts of interest in this work.

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