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Paper

Can we identify stroke sub-type without imaging? A multidimensional analysis

Abdulaziz Alshehri [a,b], Ronney B. Panerai [a,c], Man Yee Lam [a], Osian Llwyd [d], Thompson G. Robinson [a,c], Jatinder S. Minhas [a,c,*]

[a] Cerebral Haemodynamics in Ageing and Stroke Medicine (CHiASM) Research Group, Department of Cardiovascular Sciences, University of Leicester, Leicester LE1 7RH, UK
[b] Department of Emergency Medical Services, College of Applied Medical Sciences, Najran University, Najran P.O. Box 1988, Saudi Arabia
[c] NIHR Leicester Biomedical Research Centre, Leicester, UK
[d] Wolfson Centre for Prevention of Stroke and Dementia, Department of Clinical Neurosciences, University of Oxford, Oxford, UK

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ABSTRACT

Stroke is a major cause of mortality and disability worldwide, with ischemic stroke (AIS) and intracerebral haemorrhage (ICH) requiring distinct management approaches. Accurate early detection and differentiation of these subtypes is crucial for targeted treatment and improved patient outcomes. Traditionally, imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are required to distinguish between AIS and ICH. However, this study explores a non-imaging approach to differentiate between stroke subtypes. Using a retrospective dataset of 80 mild-to-moderate patients suffering stroke (68 AIS and 12 ICH), we employed principal component analysis (PCA) combined with logistic regression (LR) to evaluate 67 parameters. These parameters include baroreceptor sensitivity, and cerebral and peripheral hemodynamic variables. The PCA-LR model, validated through two-fold and six-fold cross-validation methods, effectively differentiated between AIS and ICH. BRS parameters and cerebral hemodynamic factors contributed significantly to the model's accuracy. The two-fold cross-validation approach achieved an area under the curve (AUC) of $\geq$0.92, while the six-fold method maintained a consistent variance explanation (AUC $\geq$0.79). Results suggest that this multidimensional approach may facilitate early stroke subtype identification (AIS vs ICH) without reliance on imaging, offering a promising tool for ultra-acute stroke care in prehospital settings. However, it is important to note that the model has been tested in confirmed stroke cases, and its ability to distinguish between stroke and stroke mimics remains an important limitation for broader clinical application. Future research with larger datasets is warranted to refine the model and validate its clinical applicability.

1. Introduction

Clinically, stroke is a neurological syndrome characterised by acute, focal deficits caused by vascular injury to the brain (i.e. ischemia or haemorrhage) [1]. Among the leading causes of death and disability, stroke is the second most common cause of mortality and disability-adjusted life expectancy [2]. Strokes can be classified into two general categories: ischaemic stroke (AIS) and intracranial haemorrhage (ICH), which require different management and treatment strategies. AIS account for approximately 85 % of strokes, while ICH represent the remaining 15 % [3]. Addressing the significant increase in stroke incidence requires early detection and distinction of stroke sub-types in the prehospital setting to facilitate timely targeted management [4].

Generally, the detection of stroke is based on clinical manifestations followed by neuroimaging confirmation following hospital admission. Computed tomography (CT) and magnetic resonance imaging (MRI) techniques are considered the most reliable methods for discriminating ICH from AIS [5], however the ability of characterising stroke subtypes based on cerebral and peripheral haemodynamic variables would bring in an entirely new perspective in ultra-acute stroke care. The prehospital care system plays a crucial role in stroke management in the early stages. It was in 2008 that an innovative perspective emerged for faster

* Corresponding author.
E-mail addresses: aaha7@leicester.ac.uk (A. Alshehri), rp9@leicester.ac.uk (R.B. Panerai), man.lam@uhl-tr.nhs.uk (M.Y. Lam), osian.llwyd@ndcn.ox.ac.uk (O. Llwyd), tgr2@leicester.ac.uk (T.G. Robinson), jm591@leicester.ac.uk (J.S. Minhas).

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intravenous thrombolytic therapy (IVT) delivery, referred to as the mobile stroke unit (MSU) [6]. Compared to conventional IVT, MSU reduced IVT time and provided better functional outcomes, although the cost of the MSU is considerable [7,8]. Pre-hospital stroke classification could facilitate rapid identification and appropriate treatment of patients, leading to improved outcomes for stroke patients, reducing disability, complications and mortality [9].

Previous studies have indicated that several haemodynamic parameters, namely blood pressure (BP), end-tidal carbon dioxide ($EtCO_2$), blood oxygen saturation and dynamic cerebral autoregulation (dCA) are altered or impaired following acute stroke [10–13]. In acute stroke care, cerebral and peripheral haemodynamic variables play an important role in diagnosis and treatment [10]. Due to the increasing availability of large datasets, an inverse approach could be envisaged using multiple cerebral and peripheral haemodynamic variables to differentiate between the two main types of strokes using a statistical approach. Using a relatively large dataset of previous studies on AIS and ICH, we have tested the hypothesis that it should be possible to distinguish between these two groups of confirmed stroke patients without the need for imaging data. However, it is important to acknowledge that differentiation from stroke mimics, which would be crucial in prehospital settings, has not been addressed in this analysis.

2. Methods

2.1. Patient sample

The study was based on retrospective data contained in the Leicester Cerebral Haemodynamic in Ageing and Stroke Medicine (CHiASM) database [14]. Data were extracted from 80 stroke patients whose diagnosis was confirmed with CT within 48 hours of the onset of symptoms. Each of the contributing studies was approved by the Research Ethics Committee for patient studies [15–17]. Recordings were obtained from both AIS and ICH with written informed consent from participants. Participants were $\geq$18 years of age and admitted to the Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, with mild and moderate stroke based on National Institutes of Health Stroke Scale (NIHSS $<$8). The patients were classified according to the Oxfordshire Community Stroke Project (OCSP) classification, corresponding to nine total anterior circulation strokes (TACS), thirty-three partial anterior circulation strokes (PACS), thirty-one lacunar strokes (LACS) and seven posterior circulation syndrome (POCS) [18].

2.2. Measurements

Recordings were obtained from both AIS and ICH patients, including accurate bilateral simultaneous measurements of cerebral blood velocity (CBv) in the middle cerebral artery via transcranial Doppler ultrasound (TCD) with 2 MHz probes (Viasys Companion III; *Viasys Healthcare*), secured in place with a head frame. A continuous measurement of beat-to beat mean arterial pressure (MAP) was recorded by the Finometer device (*FMS, Finapres Measurement Systems, Arnhem, Netherlands*), which was applied to the index finger of the non-hemiparetic hand of the patient. $EtCO_2$ was assessed using a capnograph (*Capnocheck Plus*) and a nasal cannula (*Salter Labs*). Heart rate (HR) was obtained using a lead II electrocardiogram.

The data were recorded continuously using the PHYSIDAS data acquisition system (*Department of Medical Physics, University Hospitals of Leicester*) at a rate of 500 samples/s. The servo-correcting mechanism of the Finometer® was turned on and off before the recordings. In addition, systolic (SBP) and diastolic blood pressure (DBP) were measured using a sphygmomanometer (OMRON) with an upper arm cuff for calibration of Finometer records. Continuous measurements lasted for at least five minutes and were visually inspected for their entire duration.

2.2.1. Data analysis

Linear interpolation was used to eliminate narrow spikes ($<$100 ms), and a median filter was applied to the recorded CBv to eliminate the remaining spikes. All signals were low-pass filtered with 8th order Butterworth filter with a cut-off frequency of 20 Hz. The R wave was automatically detected from the QRS complex of the ECG and visually inspected and manually corrected in case of any missed beats or false-detection. The beginning and end of the cardiac cycle were used to derive estimates of beat-to-beat HR, as well as mean values of MAP and CBv. The continuous, breath by breath output of the capnograph was linearly interpolated, and resampled with each cardiac cycle to generate a synchronous signal of $EtCO_2$.

Transfer function analysis (TFA) of the MAP-CBv relationship was conducted using Welch's method, using 512 samples per segment, with 50 % superposition for five-minute recordings [19]. The Fast Fourier Transform (FFT) algorithm was used to estimate the auto- and cross-spectra to derive the frequency dependent coherence function, gain and phase [19]. The inverse FFT allowed the estimate of the impulse response that was then integrated to generate the CBv response to a step change in MAP. The autoregulation index (ARI) was determined by fitting a template curve to the CBv step response according to Tiecks et al. [20,21]. The coherence function indicates the proportion of the output (CBv) power that can be linearly explained by the input (MAP) power. Furthermore, gain and phase estimation can be used to quantify dCA if the coherence is above its 95 % confidence limit [19].

A spectral analysis of spontaneous oscillations of the SBP and pulse interval (PI) was used to calculate the baroreceptor sensitivity (BRS). According to literature, the SBP and PI spectra are considered only for the low-frequency (LF) (0.04 to 0.15 Hz), high-frequency (HF) bands (0.15 to 0.4 Hz) and α- index (average $BRS_{LF} + BRS_{HF}$). On the basis of the TFA method, BRS is calculated separately for the LF and HF bands, as the average TFA modulus (gain) [22,23].

Sixty-seven haemodynamic parameters were derived including: 1) Peripheral haemodynamic parameters include mean arterial pressure (MAP), SBP, DBP, $EtCO_2$, HR and BRS parameters include BRS_{LF}, BRS_{HF}, α- index, mean gain BRS_{LF} ($mGaBRS_{LF}$) and mean gain BRS_{HF} ($mGaBRS_{HF}$). 2) Cerebral haemodynamic parameters ARI, CBv, systolic blood velocity, diastolic blood velocity and spectral power of CBv and MAP, coherence function, gain and phase. The complete list of the total 67 variables adopted is given in Supplementary Material (Table S.1).

2.2.2. Statistical analysis

All the parameters were expressed by mean values and standard deviation (SD). Initially, a histogram was used to represent each variable to test the normality parameter distributions and for identification of outliers. Then, the differences between AIS and ICH for each parameter were tested using independent *t*-test following assessment of data normality. Mann-Whitney U test was used for any parameters that were not normally distributed.

Principal Component Analysis (PCA) was performed for dimensionality reduction [24]. The original dataset was transformed into new orthogonal variables that represent linear combinations of the variables with the greatest variance, known as principal components (PCs) [25]. Logistic regression (LR) is a widely used statistical method for assessing the contribution of multiple variables to the likelihood of a binary outcome. In several clinical studies, the PCA-LR analysis model has been applied as a predictive diagnostic tool to aid in disease prevention and management [26–28]. Additionally, a cross-validation analysis was conducted in order to evaluate the performance of the prediction model in identifying stroke subtypes as it is one of the most commonly used methods of evaluating performance of predictive model [29]. In our diagnostic approach, we employed both two- and six-fold cross--validation methods. The rationale for using both methods is explained in detail in the discussion section below. With the inclusion of 68 AIS patients and 12 ICH patients, the two-fold approach resulted in each fold containing 6 ICH patients and 34 AIS patients. Comparatively, for the

six-fold method, each fold contained 2 ICH patients; four folds had 11 AIS patients each, while the remaining two folds had 12 AIS patients each. PCA was performed on the correlation matrix and PCs loadings were based on the *equamax* rotation. Significant PCs were identified as those with an eigenvalue greater than 1, and these were visually inspected using a scree plot. For the main PCs selected, the corresponding variables identified by the *equamax* rotation, were used as inputs to a logistic regression to assess their association with each of the stroke subtypes. The results of this analysis allowed identification of the physiological variables that are most influential in determining stroke subtypes. A Wald test was used to compare the best fit of each PC model among all the included PCs. The PCs with p-values lower than 0.25 were used to construct the logistic regression model. Ultimately, variables with loading coefficients greater than 0.3 were deemed to significantly contribute to each PC.

In this study, PCA-LR analysis model was adopted to discriminate between the AIS and ICH stroke groups, in light of the clinical studies mentioned above that followed the same approach. Patients were allocated to a training and testing groups, whilst maintaining the same proportion of their incidence of (AIS=85 %) and (ICH=15 %), as described in the literature [30]. A receiver-operator characteristic curve (ROC) analysis was determined to assess the performance of training diagnostic model and illustrates the relationship between the true positive rate (sensitivity) and the false positive rate (1-specificity) across different threshold settings. For each training set among both approaches, the ROC curve was used to identify the optimal threshold as the point in the curve that maximises specificity while maintaining at least 80 % sensitivity. ROC curve and the corresponding Area Under the Curve (AUC) are essential metrics for evaluating the performance of binary classification models. The AUCs quantify the overall discriminatory power of each model ranging from 0 to 1. All analyses were performed in GraphPad Prism 9.0 (GraphPad Software, San Diego, California, USA). A p-value <0.05 was adopted to represent statistical significance.

3. Results

The study included 68 AIS patients [41 males, mean ±SD age 66.8 ± 12.4 years] and 12 ICH patients [8 males, age 67.9 ± 16.2 years], with a mean NIHSS of 6.2 ± 4.6 and 3.8 ± 3.1, respectively indicating greater severity for AIS in comparison with ICH ($p = 0.04$). BRS_{LF} and $mGaBRS_{LF}$ were significantly higher in AIS than in ICH, but neither the other BRS nor peripheral physiological variables, such as the MAP, SBP, DBP, HR and $EtCO_2$, showed a significant difference between the two groups (Table 1).

Multiple differences were observed between patients suffering from AIS and ICH on cerebral hemodynamic parameters and BRS derived parameters. Systolic and diastolic velocities in the affected hemisphere (AH) were significantly higher in ICH than in AIS (76.4 ± 19.3 vs 62.4 ± 17.6 cm/s; $p = 0.01$), (30.33 ± 7.7 vs 24.8 ± 8.9 cm/s; $p = 0.02$), respectively. In the AH, the study showed significantly higher coherence functions in the AIS than ICH, for the VLF, LF and HF (0.43±0.18 vs 0.28 ±0.16, $p = 0.01$), (0.50±0.21 vs 0.34±0.17, $p = 0.01$) and (0.56±0.21 vs 0.39±0.188, $p = 0.016$) intervals, respectively. Furthermore, both groups in the unaffected hemisphere (UH) demonstrated significant higher coherence function in the AIS than ICH among LF (0.51±0.23 vs 0.28±0.18, $p = 0.002$) and HF bands (0.55±0.24 vs 0.37±0.23, $p = 0.02$), respectively. In terms of BRS estimates, $mGaBRS_{LF}$ range was significantly higher in the AIS than in the ICH (5.8 ± 5.3 vs 2.7 ± 1.8, $p < 0.001$). In the LF band, AIS had a significantly higher BRS than ICH (6.7 ± 4.2 vs 4.1 ± 2.13, ms/mmHg; $p = 0.04$). No significant differences were observed between AIS and ICH for any other derived parameters by simple univariate comparisons (Table S.1)

Table 1
Main demographic and clinical characteristics of AIS and ICH patients.

Characteristic	AIS $n = 68$	ICH $n = 12$	p-value
Age, years	66 (12)	68 (16)	0.80
Sex (male), n (%)	41 (60.3)	8 (66.7)	0.67
NIHSS admission	6.63 (4.66)	3.83 (3.18)	0.04
Time to Assessment, hours	18.64 (13.5)	24.08 (11.1)	0.19
OCSP (Stroke subtype), n (%)			
TACS:	8 (11.8)	1 (8.3)	0.72
PACS:	29 (42.6)	4 (33.3)	0.54
LACS:	27 (39.7)	4 (33.3)	0.67
POCS:	4 (5.9)	3 (25)	0.03
Systolic BP, mmHg	148.3 (27.1)	145.2 (24.6)	0.69
Diastolic BP, mmHg	81.7 (15.2)	75.3 (15.3)	0.19
MAP, mmHg	102.6 (17.5)	99.2 (15.05)	0.48
End-tidal CO_2, mmHg	33.4 (3.0)	34.9 (4.0)	0.43
Heart Rate, bpm	70.1 (13.6)	72.6 (13.6)	0.60
$mGaBRS_{LF}$	5.89 ± 5.32	2.71 ± 1.89	**0.046**
$mGaBRS_{HF}$	9.04 ± 9.37	5.94 ± 7.75	0.28
BRS_{LF}	6.7 ± 4.2	4.10 ± 2.13	**0.040**
BRS_{HF}	10.61 ± 7.56	9.06 ± 10.03	0.53
α- index	8.82 ± 5.72	6.58 ± 5.95	0.22

Values are mean (SD) or n(%), NIHSS, National Institutes of Health Stroke Scale; AIS, Acute ischemic stroke; ICH, Intracerebral haemorrhage; OCSP, Oxfordshire Community Stroke Project; TACS, Total anterior circulation stroke; PACS, partial anterior circulation stroke; LACS, lacunar stroke syndrome; POCS, posterior circulation syndrome; BP, Blood Pressure; CO_2, Carbon Dioxide; MAP, Mean Blood Pressure; BRS, Baroreceptor sensitivity; LF, Low frequency; MF, Medium frequency; HF, High frequency, Mean gain BRS_LF; $mGaBRS_{LF}$, Mean gain BRS_HF; $mGaBRS_{HF}$.
P-values for difference between ischemic and haemorrhagic stroke assessed with the independent *t*-test or Mann-Whitney U test.

3.1. PCA–LR training models

The two-fold cross-validation training sets showed that the main 16 principal components (PCs) explained 91.07 % and 89 % of the total variance, respectively. For the six-fold cross-validation training sets, the same 16 principal components accounted for 85.36 %, 85.40 %, 84.95 %, 85.40 %, 85.68 % and 84.61 % of the total variance, respectively. This indicates that while the two-fold training sets captured a higher proportion of variance, the six-fold sets maintained a more consistent explanation of variance across all folds. In each PC, variables with significant loading coefficients greater than 0.3 are given in Supplementary Material (Table S.2). The ROC curves for the training sets for both approaches are shown in Fig. 1, and the corresponding AUC values are given in Table 2 and with the LR coefficient values given in Table S.3.

In summary, for the two-fold cross-validation approach, the two training sets were primarily characterized by peripheral parameters (SBP, DBP, HR, $EtCO_2$, MAP power across all frequency ranges), cerebral hemodynamics (MCAv, systolic and diastolic velocities, coherence, ARI, gain and phase), and BRS parameters ($mGaBRS_{LF}$, $mGaBRS_{HF}$, BRS_{LF}, BRS_{HF} band and α-index), which effectively differentiated between stroke subtypes (AIS and ICH) with an AUC of ≥ 0.92 ($p < 0.001$). Additionally, in the six-fold cross-validation approach, most training models were mainly defined by peripheral (MAP, SBP, DBP), cerebral hemodynamic (MCAv, coherence, ARI, gain and phase), and BRS parameters ($mGaBRS_{LF}$, $mGaBRS_{HF}$, BRS_{LF}, BRS_{HF} band and α-index), distinguishing AIS from ICH with an AUC of ≥ 0.79 ($p < 0.001$). On the other hand, variables contributing less to the diagnostic approach included peripheral parameters ($EtCO_2$, HR and mean MAP power), cerebral hemodynamics (MCAv power, systolic and diastolic velocity), and BRS parameters (PI power and SBP power), Table S.4 highlights key variables included in each model.

3.2. PCA–LR testing

Patients were divided into two and six testing groups to validate the

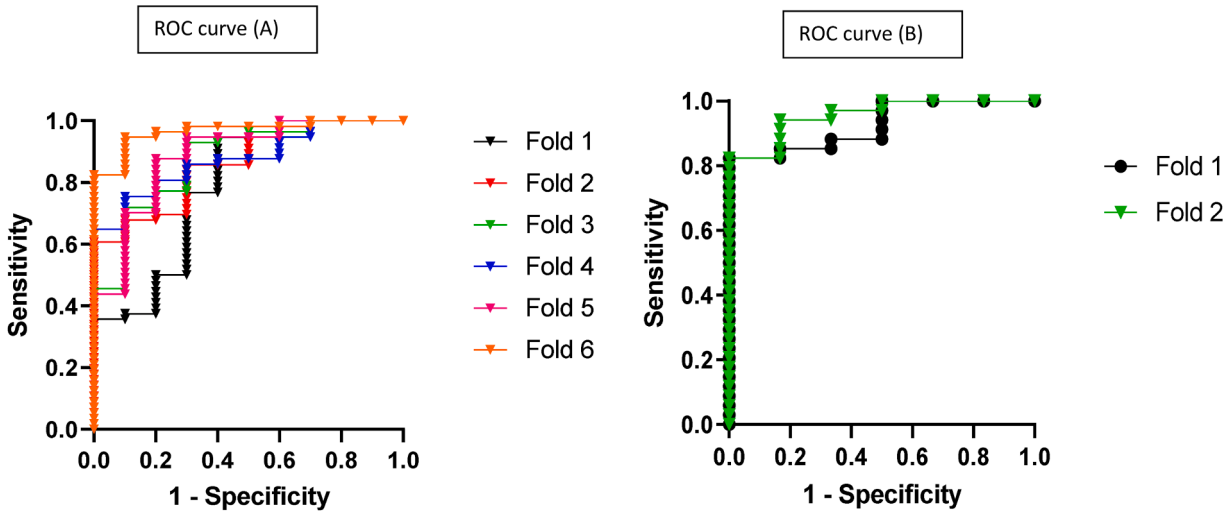

Fig. 1. (A) ROC curves of logistic regression model for the six-fold cross validation, (B) ROC curves of logistic regression model for the two-fold cross validation.

Table 2
Classification values for training sets for stroke subtypes diagnostic model.

Fold	Threshold	Sensitivity	Specificity	AUCs
Two-fold cross-validation analysis				
1st	>0.899	29/34 (85 %)	5/6 (83.3 %)	0.926
2nd	>0.853	28/34 (82 %)	5/6 (83.3 %)	0.955
Six-fold cross-validation analysis				
1st	>0.716	51/56 (91 %)	6/10 (60 %)	0.792
2nd	>0.822	48/56 (85 %)	7/10 (70 %)	0.866
3rd	>0.874	44/57 (77 %)	8/10 (80 %)	0.875
4th	>0.877	42/57 (73 %)	9/10 (90 %)	0.877
5th	>0.772	50/57 (87 %)	8/10 (80 %)	0.886
6th	>0.757	53/57 (92 %)	9/10 (90 %)	0.966

training models. The probability for each group was predicted, and the threshold for these groups was set to maximize both specificity and sensitivity, as previously described. Table 3 presents the sensitivity and specificity values for the testing folds in the analysis of the diagnostic model's performance across stroke subtypes, the models demonstrated a higher sensitivity in detecting AIS compared to ICH. These findings suggest that the model is better optimized for recognizing the patterns associated with AIS, while its performance in detecting ICH remains less robust.

4. Discussion

4.1. Main findings

In our preliminary analysis, we employed a PCA-LR diagnostic model to identify the most significant clinical variables that reliably distinguish between AIS and ICH. The model's performance was extensively assessed using both a two-fold and a six-fold cross-validation approach. Our multi-dimensional approach indicated that BRS parameters ($mGaBRS_{LF}$, mGaBRSHF, BRSLF, BRSHF band and α-index), cerebral haemodynamic parameters (MCAv, coherence, ARI, gain and phase) and peripheral (MAP, SBP, DBP) as key parameters in discriminating between stroke subtypes which consistently contributed to most of the training sets. Furthermore, the diagnostic model received a comparatively lower contribution from peripheral variables ($EtCO_2$, HR and mean MAP power), cerebral hemodynamic variables (MCAv power, systolic and diastolic velocity), and BRS parameters (PI power and SBP power).

Table 3
Classification values for testing sets for stroke subtype diagnostic models.

Fold	Threshold	Sensitivity	Specificity
Two-fold cross-validation analysis			
1st	>0.899	27/34 (79 %)	5/6 (83.3 %)
2nd	>0.853	27/34 (79 %)	3/6 (50 %)
Six-fold cross-validation analysis			
1st	>0.716	12/12 (100 %)	0/2 (0 %)
2nd	>0.822	10/12 (83.3 %)	1/2 (50 %)
3rd	>0.874	7/11 (63.6 %)	1/2 (50 %)
4th	>0.877	3/11 (27.2 %)	2/2 (100 %)
5th	>0.772	8/11 (72.7 %)	1/2 (50 %)
6th	>0.757	11/11 (100 %)	0/2 (0 %)

For each fold, the threshold is the probability value provided by the LR output to detect patients as having AIS. AUC: area under the Receiver Operator Curve.

4.2. Methodological considerations

In the development of our preliminary diagnostic model, we employed both two-fold and six-fold cross-validation approaches to discriminate stroke subtypes, aiming to provide a robust evaluation of model performance and generalizability. The two-fold model, with its simpler data split, allows for larger representation of ICH patients in the training sets, enabling the model to capture a more comprehensive understanding of key features, resulting in a higher AUC value, which reflects its strong discriminatory power. However, this approach may risk overfitting due to fewer divisions of the data. On the other hand, the six-fold model, with a more granular division of the dataset, increases the opportunity for model generalisation by testing on a greater variety of data subsets. By repeating the process across all folds, we minimised the risk of overfitting and ensured that our model's performance was thoroughly tested on various subsets of the data [31]. These two complementary testing approaches provided a more reliable estimate of the model's diagnostic accuracy and helped identify any potential weaknesses when applied to new, unseen data, thereby enhancing the overall robustness of our classification approach. Together, these approaches allow for a balanced assessment of feature significance and model robustness, offering insights into the distinct roles of peripheral, cerebral hemodynamic, and BRS parameters in stroke subtype classification.

PCA - LR models were previously used to predict patient's disease states and clinical outcomes [27,28,32]. In 2014, Milewska et al. developed an effective prediction model for pregnancy outcomes in patients undergoing in vitro fertilization [27]. Huang et al. identified key clinical factors associated with lupus nephritis in patients with hypothyroidism [28]. Similarly, PCA-LR models were adopted to predict sudden death using diagnostic data from emergency departments,

demonstrating that they performed better than LR models alone [32]. Accordingly, we utilised a PCA-LR analysis to construct a predictive approach capable of describing stroke subtypes (AIS and ICH). Through the integration of the PCA-LR analysis model, we were able to reduce the dimensionality of the data and identify the most relevant clinical variables for stroke subtyping, namely BRS, cerebral haemodynamic and peripheral parameters.

4.2.1. BRS

In this study, non-invasive BRS was evaluated in stroke patients suffering from AIS and ICH. Our findings suggest that BRS estimates are crucial for distinguishing between stroke subtypes. Previous research has highlighted the predictive value of BRS in various disease states, emphasising its potential as a biomarker for multiple health conditions [33–35]. Robinson et al. identified a connection between reduced BRS and long-term mortality, age, stroke severity and subtypes in AIS patients [33]. Additionally, BRS has been widely investigated for its prognostic significance in myocardial infarction patients [34]. A key outcome of this prospective study is the independent prognostic value of BRS for mortality in those patients. Moreover, the relationship between BRS, metabolic syndrome and insulin resistance in elderly patients was examined, revealing that BRS is impaired in metabolic syndrome and inversely correlated with insulin resistance [35]. The consistent predictive value of BRS across different diseases underscores its significance as a non-invasive biomarker, and BRS parameters can be utilized to guide clinical decision-making and enhance patient outcomes. As demonstrated in this study, BRS indices emerged as essential components in a diagnostic model used to differentiate stroke subtypes.

4.2.2. Cerebral haemodynamic parameters

Furthermore, the alterations in cerebral haemodynamic parameters and their impacts on various diseases have been extensively documented [36,37]. Recent comprehensive systematic reviews have investigated the role of CA in cerebrovascular disease [38] and non-brain injured populations [39]. According to Al-Kawaz et al. [38], examination of 48 records on the impact of CA on various cerebrovascular disease populations, including 23 studies on AIS, 5 studies on ICH, 18 studies on subarachnoid haemorrhage and two studies on systemic hypertension. The study found that CA impairment among various cerebrovascular conditions was consistently associated with poor functional outcomes and larger infarct sizes and haemorrhagic transformation in AIS. The CA in AIS was preserved during the early phase after stroke, which was associated with improved functional outcomes and smaller insults, and was used to predict the response to thrombolysis therapy. A study conducted by Longhitano et al., [39] examined the role of CA in several medical populations, including sepsis, paediatrics, and during surgery. Twenty-two studies demonstrated that impaired CA can lead to increased mortality, morbidity, neurological damage and cognitive impairment. Additionally, a recent large meta-analysis including 384 patients found that the dCA of the AH is associated with poor functional outcomes at the early stage of AIS [40]. As several CA parameters are highly predictive of functional outcomes, reinforcing the necessity to implement early CA-guided interventions during the ultra-acute phase would be an advantage to use in a stroke subtype discrimination model, as shown in our current study, which demonstrated that several dCA variables were key inputs to our diagnostic model.

4.2.3. Peripheral haemodynamic parameters

A systematic review investigated current practices and evidence related to peripheral physiological monitoring in prehospital stroke care. The review found that BP parameters, including SBP, DBP and MAP, are the most commonly studied factors in this context. The study also revealed a significant link between these BP parameters and both neurological deterioration and larger hematoma volumes in cases of ICH [41]. Moreover, $EtCO_2$ values were evaluated in patients who underwent endovascular thrombectomy following AIS. A prospective study by Sheriff et al. demonstrated the importance of monitoring $EtCO_2$, as it was shown that $EtCO_2$ values were higher in larger strokes and tended to remain higher for 96 hours in incomplete recanalization [42]. Consequently, our study determined that multiple peripheral parameters, which play an important role in discriminating stroke subtypes, align with previous findings on the critical role of peripheral variables in acute stroke care.

Despite the well-established role of cerebral haemodynamic parameters, BRS and peripheral variables in predicting functional outcomes after the incident stroke, there is a significant lack of evidence supporting their value in distinguishing between AIS and ICH. These physiological variables have demonstrated their effectiveness in prognosis and recovery after stroke. Our preliminary results are promising and suggest that our approach could potentially enhance the ability to discriminate between stroke subtypes. This work should be viewed as a signposting exercise, offering valuable insights and a foundation upon which future research can build. As a result of refining the methodologies, such as implementing longer recordings with higher BP variability and expanding the sample size, subsequent studies may provide the required evidence to integrate these approaches into clinical practice, with the potential to improve stroke patient outcomes.

4.3. Clinical perspectives

There has been a noticeable improvement in ultra-acute stroke care, specifically prehospital diagnosis and management, following the introduction of MSUs aligned with point-of-care imaging which typically include a CT scanner, a point-of-care laboratory and telemedicine capabilities to connect with stroke specialists remotely [43]. It is unfortunate that these advancements face a number of challenges, such as limited resources in low-income countries and geographic barriers that make them critical for broader adoption. Therefore, multiple portable devices for detecting stroke subtypes have been introduced, for instance portable transcranial Doppler ultrasound which indicated reasonable level of sensitivity and specificity for subtyping stroke in the prehospital setting [44]. A recent study presented an ultrasound-based triage model for detecting stroke subtypes, which combined transcranial ultrasound with clinical assessment. This integrated approach resulted in a 10 % improvement in the detection of ICH compared to relying solely on clinical assessment [45].An observational study conducted in the prehospital setting identified significant physiological differences between stroke mimics and actual strokes, including variations in blood glucose levels, BP, body temperature, oxygen saturation and HR [46]. According to a preliminary study, there were alterations in several haemodynamic variables between ICH and AIS including CA and BRS [47]. As highlighted in the study emphasizing the need for multivariate statistical modelling to characterize stroke subtypes, this research explored the effectiveness of PCA-LR model as a tool for predicting stroke subtypes. A key consideration for translating our findings into clinical practice is the feasibility of acquiring BRS and cerebral hemodynamic parameters in a pre-hospital setting. BRS can be estimated using non-invasive, beat--to-beat blood pressure monitoring systems such as Finometer device, which are compact and potentially suitable for use in mobile environments like ambulances. Cerebral hemodynamic parameters particularly CBv and autoregulation indices are typically assessed using TCD. TCD has been proposed for prehospital large vessel occlusion detection, with preliminary in-hospital studies demonstrating high diagnostic accuracy [48]. It is relatively compact and affordable, making it a promising tool for emergency settings. However, field implementation is currently limited by long acquisition times and the requirement for trained personnel to perform measurements and interpret results.

To address these limitations, logistical and training considerations must be explored. For example, the feasibility of incorporating BRS and TCD-based assessments into prehospital stroke protocols alongside established tools NIHSS should be evaluated. Paramedics and MSU teams would likely require training for device operation and data

acquisition. However, advances in automation and algorithm-driven interpretation could help reduce user dependency and simplify implementation. These developments could enhance the practicality of using physiological markers to support early stroke sub-type differentiation in prehospital care.

We are not aware of any previous studies attempting to predict stroke subtypes based on a variety of hemodynamic variables. The study found that the PCA-LR model effectively captured the complex interactions among multiple variables and improved stroke subtype prediction. However, the model's performance might be further enhanced by including data from patients with a broader range of stroke severity and increasing the number of stroke cases. This approach would enable the model to better capture the full spectrum of stroke severity, thereby improving its predictive power across all stroke subtypes. A future prospective study is required to validate the model with larger datasets of stroke subtypes at an earlier time point (4 hours after onset of symptoms). Additionally, it will be important to evaluate the model's ability to distinguish between stroke and stroke mimics to enhance its utility in prehospital settings. In future studies, incorporating more specific metrics that evaluate both the myogenic and metabolic components of CA could greatly improve the diagnostic model for differentiating between stroke subtypes, particularly since myogenic responses are often impaired in AIS [49,50]. Our primary diagnostic approach typically relies on generalised parameters that may not accurately reflect the distinct differences in CA responses across various stroke subtypes. By adopting a more detailed approach, a deeper understanding of the pathophysiological mechanisms associated with each stroke subtype is achievable. This could result in more precise classification tools, ultimately enhancing patient outcomes through more targeted therapeutic strategies.

In addition to traditional methods, alternative techniques such as time-lagged recurrent neural networks can be employed to model dCA more effectively by capturing its temporal dynamics [51]. Another valuable approach involves using a mathematical model to derive a quantitative autoregulation index based on the slope of the relationship between velocity pulse amplitude and cerebral perfusion pressure [52]. This model could be instrumental in exploring the interactions of multiple variables, offering new alternatives for distinguishing between AIS and ICH, providing the potential to improve predictive accuracy for stroke subtypes compared to conventional methods.

4.4. Limitations of the study

There are multiple limitations in our study. The sample size was 80 participants, and the data were collected retrospectively. This small sample size is particularly evident in the ICH group. In our study, 15 % of the participants had ICH, while 85 % had AIS. This distribution is epidemiologically based and represents the prevalence seen in emergency settings in the Western world. Additional prospective studies involving a more diverse cohort including broader mixed-sex are required to validate and extend the current findings. Cross validation, particularly when using a small dataset as the case in our study, can result in high variance in performance. In a small dataset, each fold used for cross-validation contains fewer samples leading to cause significant fluctuations in the performance metrics (Table 2). An important limitation of this study is the homogeneity of stroke severity. The lack of representation of severe stroke cases restricts the broader applicability of the findings. Additionally, the estimation of CBF based on CBv measurements in the MCA is only valid if the diameter of the MCA remains constant.

In the context of improving diagnostic models for stroke subtypes, it is important to consider the use of CA estimates obtained at rest, which may rely on spontaneous fluctuations. While these spontaneous fluctuations can provide valuable insights into CA function, their reliability and reproducibility of derived indices may be limited. To address this limitation, incorporating other manoeuvres could potentially yield more robust and reliable CA indices [36].

5. Conclusions

In conclusion, the study successfully developed a predictive model for stroke subtypes utilising Principal Component Analysis combined with logistic regression applied to a relatively large and diverse set of hemodynamic parameters and indices. This approach allowed for dimensionality reduction, effectively capturing the most critical variables and demonstrated an encouraging performance in discriminating stroke subtypes (AIS and ICH). These outcomes underscore the potential of such an approach in enhancing the reliability of stroke classification and designing patient-specific treatment modalities. Despite the preliminary nature of this study, encouraging initial results warrant further investigation adopting larger and more diverse datasets and the inclusion of additional clinical variables.

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Ethical approval

Not required.

CRediT authorship contribution statement

Abdulaziz Alshehri: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Ronney B. Panerai:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Man Yee Lam:** Data curation, Writing – review & editing. **Osian Llwyd:** Data curation, Writing – review & editing. **Thompson G. Robinson:** Conceptualization, Writing – review & editing. **Jatinder S. Minhas:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.medengphy.2025.104364.

Data availability

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

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