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Predicting symptomatic intracranial haemorrhage in acute ischemic stroke: introduction to a clinical-radiological and mri-based machine learning approach

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**PREDICTING SYMPTOMATIC INTRACRANIAL HAEMORRHAGE IN ACUTE
ISCHEMIC STROKE: INTRODUCTION TO A CLINICAL-RADIOLOGICAL AND
MRI-BASED MACHINE LEARNING APPROACH**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE

DIPLÔME D'ÉTAT

Florent LEPILLIET

[Données à caractère personnel]

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Abbreviations

AF – Atrial Fibrillation

AIS - Acute Ischemic Stroke

CT - Computerized Tomography

DM – Diabetes Mellitus

HBP – High Blood Pressure

HI – Haemorrhagic Infarction

HT – Haemorrhagic Transformation

ICH – Intracranial Haemorrhage

IVT – Intravenous Thrombolysis

ML – Machine Learning

MRI - Magnetic Resonance Imaging

mRS – Modified Rankin Scale

MT – Mechanical Thrombectomy

NIHSS - National Institute of Health Stroke Scale

OTT – Onset-to-Treatment Time

PH – Parenchymal Hematoma

sICH – Symptomatic Intracranial Haemorrhage

tPA – Tissue Plasminogen Activator

Résumé :

L'infarctus cérébral (IC) est l'une des principales causes de décès et d'invalidité. Les thérapies de reperfusion, thrombolyse intraveineuse (TIV) et thrombectomie mécanique (TM), améliorent le pronostic des patients victimes d'IC mais augmentent le risque de transformation hémorragique (TH) du parenchyme cérébral infarci. La TH symptomatique (THs) est la définition la mieux corrélée à un mauvais pronostic. Plusieurs méthodes basées sur des données cliniques et/ou radiologiques ont échoué à prédire le risque de THs en pratique clinique. Nous avons élaboré un algorithme d'apprentissage machine supervisé (ML) sur des données cliniques et d'IRM au sein d'une cohorte de 100 sujets atteints d'IC de circulation antérieure traités par TIV et/ou TM. Certains ont présenté une THs (n=28) ou une TH non symptomatique (n=27) et 45 témoins sans saignement ont été appariés sur la gravité clinique et l'âge. Nous avons comparé la performance de l'algorithme ML à celles du score clinique THRIVE (Total Health Risks in Vascular Events) et au score radiologique ASPECT (Alberta Stroke Program Early CT Score) appliqué à l'imagerie IRM (DWI-ASPECTS). L'algorithme ML a prédit la THs avec une aire sous la courbe ROC (AUC) de 0,658. Les AUC estimées du score THRIVE et du DWI-ASPECTS étaient respectivement de 0,664 et 0,634. L'algorithme ML a réussi à synthétiser les données cliniques et radiologiques pour fournir une probabilité de THs équivalente à celles des scores actuels. Des travaux complémentaires sont nécessaires pour améliorer ces performances en élargissant les effectifs, intégrer des données clinico-radiologiques plus pertinentes puis valider ces résultats sur une population hétérogène.

Mots-clés : intelligence artificielle, IRM, thrombolyse, thrombectomie, transformation hémorragique

Abstract:

Acute ischemic stroke (AIS) is a leading cause of death and disability. Reperfusion therapies using intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) improve functional outcomes in patients with AIS but unfortunately increase the risk of intracranial haemorrhage (ICH) of ischemic brain tissue. Symptomatic ICH (sICH) is the most relevant definition as it is most correlated with poor outcome. Several methods, based on clinical and/or radiological data, failed to predict the risk of sICH in clinical practice. We attempted a new approach by training a supervised machine learning (ML) algorithm on clinical and MRI data within a 100 subjects cohort of patients with anterior circulation AIS treated by IVT and/or MT who underwent sICH (n=28), non-symptomatic ICH (n=27) and 45 controls with no bleeding, matched on clinical severity and age. We compared ML algorithm accuracy to the performance of the clinical Total Health Risks in Vascular Events (THRIVE) score and to the radiological Alberta Stroke Program Early CT Score applied to MR imaging (DWI-ASPECTS). ML algorithm predicted sICH with an Area Under receiver operating characteristic Curve (AUC) of 0.658. Estimated AUC of THRIVE score and DWI-ASPECTS were 0.664 and 0.634, respectively. Although it does not outperform current tools, ML algorithm was able to synthesize clinical and radiological data to provide a sICH probability. Further studies are needed to improve these performances. Enlarging dataset and integrating more relevant clinical and radiological data should be the first avenues for improvement. Validation of these results on a more heterogeneous external population is also warranted.

Keys words: machine learning, deep learning, MRI, thrombolysis, thrombectomy, symptomatic haemorrhagic transformation

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1. Introduction

Stroke is a leading cause of death and disability in adult. Ischemic stroke is the most common type of stroke with a global life-time risk of 18% (1). Reperfusion therapies using intravenous thrombolysis (IVT) and endovascular interventions such as mechanical thrombectomy (MT) are timely restricted but improve functional outcomes in patients with acute ischemic stroke (AIS) (2–4). Unfortunately, these therapeutics increase the risk of haemorrhagic transformation of ischemic brain tissue (4–6), also called intracranial haemorrhage (ICH). The symptomatic intracranial haemorrhage (sICH) is defined as a neurological deterioration concomitant to an intracranial haemorrhage after reperfusion therapies. Radiological definitions of ICH are classically based on the opposition between haemorrhagic infarction (HI), which corresponds to haemorrhagic petechiae within the ischaemic area, and intra-parenchymal haematoma (PH), which represents a haemorrhagic area with clear sides with or without a mass effect (7). Because of different definitions of sICH in randomized clinical trials and prospective registries, incidence of sICH is ranged between 2-7% after reperfusion therapies (8–10). Rates of sICH are significantly reduced after IVT using MRI-guide selection of patients, ranging from 2 to 3% (3,11,12). sICH is strongly associated with 3-months poor functional outcomes and mortality (13).

1.1. Pathophysiology and risk factors

ICH seems to be part of the natural history of ischemic infarction and could be worsen by reperfusion therapies. Numerous clinical factors have been identified as potential risk factors for ICH, such as age (6); high blood pressure (6) ; hyperglycemia (14) ; atrial fibrillation (15); clinical severity based on NIHSS (16) ; delay of treatment (17) and used of antithrombotic treatments (antiplatelet and anticoagulant agents) (18).

Meanwhile, some radiological data have been identified of interest to predict ICH. The presence of early ischemia signs on CT scan has been well identified as a risk factor for ICH (7,19). Large vessel occlusion (LVO) reflected by hyperdense middle cerebral artery sign on CT scan has also been suggested as independent predictive factor (20). Regarding MR-based imaging, which tends to become a gold standard for management of AIS, increasingly works are conducted on its contribution to ICH prediction. MR imaging provides a wide range of morphological information of ischemic lesion and adjacent parenchyma tissue which could be predictive of ICH such as apparent diffusion coefficient value (21), FLAIR hyperintensities (22), visible leukopathy in FLAIR (23), microbleeds burden visible on T2* sequence (24). But brain infarction volume on DWI appears as an independent and strongest risk factor of ICH compared to others factors (25).

Post-thrombolytic haemorrhagic transformation depends on multiple and interconnected pathological processes, including ischaemic lesions and coagulopathy. Quantifying the risk of sICH would be a valuable aid for clinicians to guide therapeutic decision.

1.2. Prediction scores

Several scores aimed to predict sICH mixing clinical and radiological data, which showed similar predictive values (26–28). These are rarely used in current practice because there is not enough confidence in their prediction to generally justify a deferral of thrombolysis when high-risk patients are often those whose prognosis would be bleakest without thrombolysis (29). None of these scores are based on initial MRI. The Total Health Risks in Vascular Events (THRIVE) score appears as the most practical and robust (30). The THRIVE score assigns 1 point for 60 to 79 years of age, 2 points for ≥ 80 years of age, 2 points for NIHSS score 11 to 20, 4 points for NIHSS score ≥ 21 , and 1 point each for hypertension, DM, and AF. The Alberta Stroke Programme Early CT Score (ASPECTS) is 10 points score originally based on early

ischaemic changes identified on CT during the first few hours after stroke onset, representing early cytotoxic oedema and possibly the development of irreversible injury. It was significantly correlated to functional outcome and predicts sICH with sensitivity and specificity values of respectively 0.90 and 0.62 (31). A threshold of 7 has been identified as most relevant (19). In routine practice, DWI-ASPECTS is used to identify patients with acute stroke and large DWI lesions, avoiding the need for measuring lesion volumes in the acute setting. The risk of sICH after IVT is inversely correlated to DWI-ASPECTS and a cut-off at 7 remained the most relevant (32).

1.3. About machine learning

Artificial Intelligence (AI) refers to computer systems able to perform tasks normally requiring human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages. One of the most widely used method is machine learning (ML) whose goal is to build data analysis algorithms to extract characteristics from these data. This technique generally involves two phases. A “training phase” aimed at training the algorithm to perform a task (classification, segmentation) on a selected database. The task can be provided to the algorithm (supervised learning) or must be deduced by the algorithm itself (unsupervised). The second phase called "testing phase" aims at using the previously established model to process new unknown data.

The supervised machine learning method consists in learning a function that maps an input to an output based on a labelled training set of data, composed of input-output pairs. A supervised ML algorithm analyses the training data, learns from previous mistakes after repeated analysis, and produces an inferred function, which can be used for mapping new examples. The optimal scenario will allow for the algorithm to correctly determine the class labels for unseen instances. The most popular technique currently used is Artificial Neural Network (ANN). ANN is

inspired by biological neural networks: an artificial neuron receives inputs from other neurons, integrates inputs that are weighted and activates when a defined condition is met. This method is very flexible and applicable to a wide variety of characteristic data. Concerning imaging data, it consists of performing multiple statistical tests (regression) in each voxel without selection in order to select the most relevant characteristics.

Deep Learning is a recent refinement of neural networks that mimics the human brain using multiple layers of neural networks, interconnected in different ways depending on the type of network (Convolutional Neural Network, Recurrent Neural Network...). This was made possible thanks to the improvement of computer techniques, processing power and management of Big Data. The ability for such algorithms to manage various kinds of data (quantitative, qualitative, non-linear...) and the amount of data currently collected in our hospitals, explains the recent craze in the medical world and the exponential number of publications in the medical field referring to such techniques, mainly in the field of medical imaging (33–35). Having regard to stroke management, researchers recently attempt to improve stroke imaging using ML algorithm in various ways : automatically detection of infarcted area (36), segmentation (37), prediction of the final infarcted area (38), prediction of the clinical outcome (39).

Prediction of upcoming ICH occurrence using ML has recently provided encouraging results when based on clinical variables (40), CT images (41) or permeability parameters derived from PWI (42), some models can even be used to predict territory and extent of ICH, using a voxel to voxel analysis (43).

The algorithm implemented in this work is based on supervised learning using an ANN. In the brain, neurons exchange information via chemical and electrical synapses. Electrochemical signals are propagated from the synaptic area through the dendrites when a certain excitation threshold is reached, the cell then releases an activation signal through its axon toward synapses

with neighbouring neurons. Complex signals can be encoded by networks of neurons based on this paradigm; for instance, a hierarchy of neurons in the visual cortex is able to detect edges by combining signals from independent visual receptors. ANN are inspired by this biologic process. The basic unit of an ANN, the artificial neuron or node, is a simplified model that mimics this basic mechanism. The artificial neuron takes as an input a set of values representing features, each multiplied by a corresponding weight. The weighted features are summed and passed through a nonlinear activation function. In this way, an artificial neuron can be viewed as producing a decision by weighting a set of evidence (Figure 1).

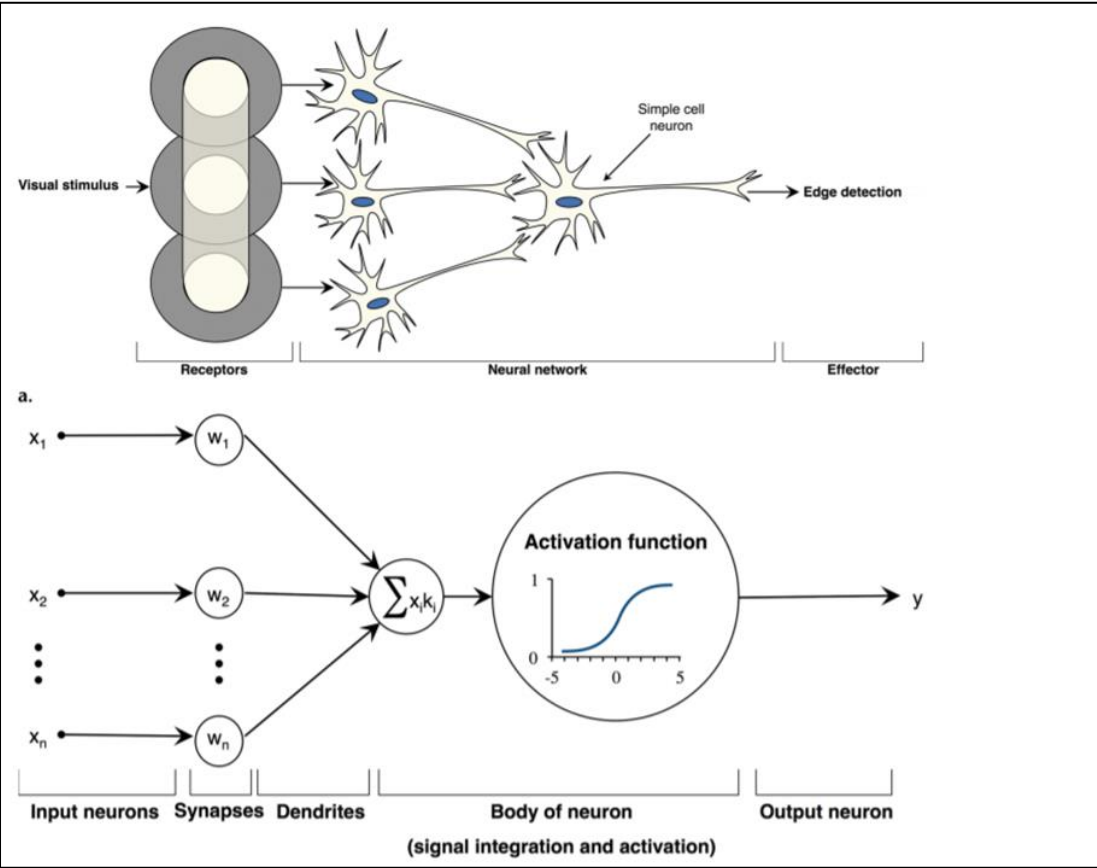


Figure 1: Conceptual principles of ANN. Deep Learning: a primer for radiologists. Chartrand et al. Radiographics 2017

Thousands of neurons assembled together form a layer. Stacking these layers, connecting the output of one layer to the input of the following layer, form the global neural network architectures which can represent very complex nonlinear functions.

The first layer, called the input layer, represents input data such as here individual pixel intensities or clinical data materialized by either categorical or continuous data. The output layer produces target values such as a classification result. The intermediate layers are called hidden layers, since they do not directly produce visible desired outputs, but rather compute intermediate representations of the input features that are useful in the inference process. A neural network is trained by adjusting the parameters, which consist of the weights and biases of each node. Starting from a random initial configuration, the parameters are adjusted via an optimization algorithm which attempts to find a set of parameters that performs well on a training dataset. For each data sample, the performance of the network is assessed through a loss (error) function that quantitatively measures the inaccuracy of the prediction (Figure 2). Each parameter of the network is then adjusted by small increments in the direction that minimizes the loss, a process called back-propagation. This training procedure is performed multiple times for each sample in the training dataset, so the parameters approach values that maximize the model accuracy (44).

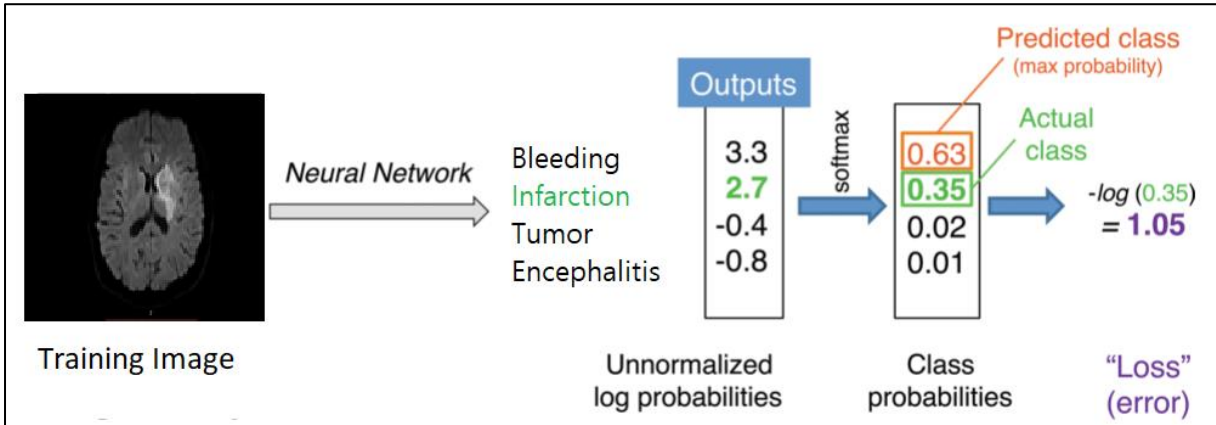


Figure 2: Prediction learning and "loss" function principle.

Convolutional Neuron Network (CNN) is a subclass of neural networks which have at least one convolution layer. Mathematically, a convolution is a mathematical operation which, for two input signals, produces a new signal which is a function of the two previous ones. A convolution unit receives its input from multiple units from the previous layer which together create a proximity. Therefore, the input units (that form a small neighbourhood) share their weights. The convolution units are especially beneficial as they reduce the number of units in the network (since they are many-to-one mappings). This means, there are fewer parameters to learn which reduces the chance of overfitting as the model would be less complex than a fully connected network. Moreover, they consider the context/shared information in the small neighbourhoods. This feature is very important in many applications such as image, video, text, and speech processing/mining as the neighbouring inputs (eg pixels, frames, words, etc). That is why this subclass of ANN is widely used in medical imaging field to extract features from the image by groups of pixels and finally simplify the image into a single set of features which can then be integrated in one or several last “fully connected” linear layers (Figure 3).

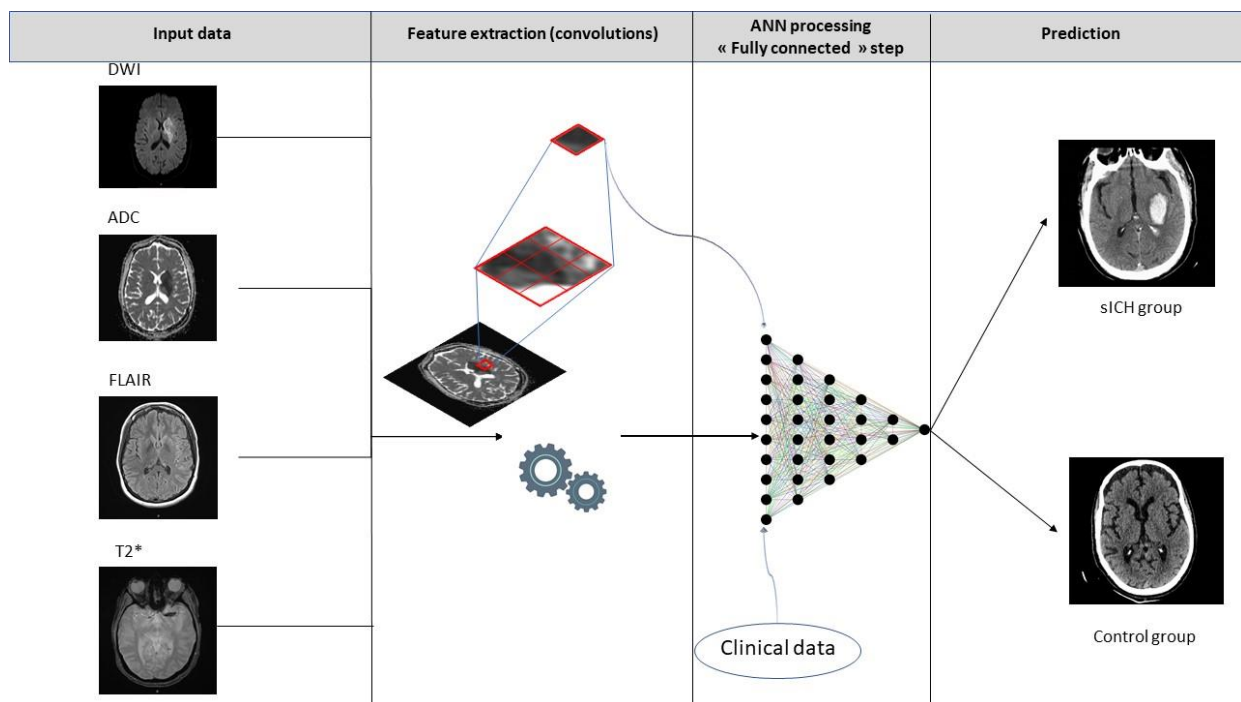


Figure 3: Overall machine learning (ML) processing scheme

A particular CNN subtype Residual Network algorithm was used here. Residual Networks (also called ResNet) are built to use “skip connections”, or “shortcuts” to jump over some layers. This kind of ANN have empirically shown to increase classification performance by simplifying the network, especially when increasing the number of layers.

1.4. Objectives

We aim to (1) evaluate a clinical-radiological MRI-based ML algorithm to predict the occurrence of a sICH and (2) compare ML algorithm accuracy to validated clinical and radiological scores performances.

2. SUBJECTS AND METHODS

2.1. Study population

Our study retrospectively analysed data from a prospective stroke registry of individual data (Northern French Alps Emergency Network, RENAUS Stroke database). We selected all AIS patients referred to Grenoble University Hospital (CHUGA) and Chambéry Hospital (CHMS) between January 2014 and December 2018 with a sICH after a reperfusion therapies which was IVT, MT or “bridging” which is a combination of IVT then MT. We matched controls with non-symptomatic ICH (1:1) and controls without ICH (1:2) on age and initial stroke severity based NIHSS score.

Symptomatic ICH was defined, according to the ECASS II definition, by an increase in the NIHSS of more than 3 points concomitant with the appearance of haemorrhagic infarction or

intra-parenchymal haematoma on the control imaging which can be either CT or MR scanner carried out within 36h, or death due to this haemorrhagic transformation.

All patients treated with IVT received ALTEPLASE with a 0.09 mg/kg bolus followed by 0.81 mg/kg infusion in one hour.

Exclusion criteria were no pre-treatment imaging available; no control imaging available; posterior circulation stroke; MT failure in patient with contraindication of IVT.

2.2. Clinical data collection

For each patient, the following data were extracted from computerized medical file and collected in a prospective registry: National Institutes of Health Stroke Scale (NIHSS) at admission (0 to 42, the severity increasing proportionally to the score); Onset-to-Treatment Time (OTT) defined as delay between stroke recognition and IVT administration or groin puncture in case of MT; medical history of high blood pressure, diabetes mellitus or atrial fibrillation; prior use of antithrombotic treatment; lateralization of the lesion; LVO as defined by intracranial carotid or first segment of middle-cerebral-artery occlusion; acute treatment carried out; modified Rankin Scale (mRS) score at discharge. Functional independence at discharge was defined as a mRS between 0 and 2.

2.3. Imaging

We only included MRI-based AIS patients. Each subject underwent a MR imaging routine protocol including diffusion-weighted imaging (DWI) b0/b1000; automatically calculated apparent diffusion coefficient (ADC) maps; Fluid Attenuated Inversion Recovery (FLAIR), flow-sensitive time-of-flight (TOF); T2*-gradient-echo. MR scanner model depends on centre

and year of acquisition: Philips Achieva 1.5T, Philips Achieva 3T, Philips Achieva-dStream 3T, SIEMENS Skyra 3T, SIEMENS – Aera 1.5T. Thus, MRI parameters: Repetition Time (TR), Echo Time (TE), slice thickness, flip angle, Inversion Time or resolution were heterogeneous.

DWI-ASPECTS on each baseline MRI was visually calculated by a neurologist according to the ASPECT study group method (31) (i.e, ASPECTS value was calculated from two standard axial DWI-MR slices, one at the level of the thalamus and basal ganglia, and one just rostral to the ganglionic structures). Radiological outcomes (HI, PH1, PH2) was collected in control imaging's radiologists report or assessed by a neurologist.

Anonymization process and data sharing

The imaging data were extracted from the central server after anonymization. Correspondence between anonymization number and patient identity was held only by the main investigators. The files were extracted into standardized compressed DICOMDIR format and then transferred to the secure and anonymized SHANOIR database (<https://project.inria.fr/shanoir/>). A standardized file containing the above-mentioned clinical data was attached to the imaging data for each patient. These data were then manipulated by the engineers and processed by the algorithm in a totally anonymous and secure way.

Imaging pre-processing

A noise reduction technique was applied. All MRI contrasts have been reframed together (patient by patient) and then reframed on a shared template. Then, brains were extracted, and images resized to get the same geometry (voxel size and section thickness).

2.4. Machine learning algorithm

A ResNet algorithm was used in this work.

The common architecture of ResNet algorithms is freely available online (https://www.tensorflow.org/api_docs/python/tf/keras/applications/resnet). It was composed of convolutional layers preceding “fully connected” linear layers (Figure 3). In order to compensate for the imbalance between the two groups thus formed (n=28 versus n=72), a different weighting has been applied to the two classes within the loss function used into the algorithm. Class weights applied to control group values and sICH group values was respectively 1.39 & 3.57. The binary-cross entropy loss function integrated inside the algorithm

can be expressed as follows:

$$H_p(q) = -\frac{1}{N} \sum_{i=1}^N y_i \cdot \log(p(y_i)) + (1 - y_i) \cdot \log(1 - p(y_i))$$

The cohort was designed into two groups according to prediction attempted: sICH group consisted of symptomatic intracerebral haemorrhage (sICH) subjects while a second was formed by merging both non-symptomatic ICH and No ICH groups to constitute one single control group.

A cross-validation (CV) approach has been used. Briefly, the dataset was randomly partitioned into 10 equal size subsamples. A single subsample is retained as the validation data, 2 subsamples are retained as the testing data and the remaining 7 subsamples are used as training data. The validation process is then repeated 10 times, with each of the 10 subsamples used exactly once as the validation data. The results (n=10) can then be averaged to produce the final estimation. The CV is an efficient way for validating a model and for assessing how it will generalize to an independent data set. These applied techniques allow to avoid bias that would otherwise occur if the performance were assessed on the same data that trained the model. The algorithm, after training, attributed to each slice a value which could be used as a threshold to

classify this slice in either group (sICH or control). In order to obtain a clinically relevant patient-level result, we averaged the probability of each slice for the same patient to obtain a single probability per patient. We then varied the probability threshold to find the one which gave the best ranking performance.

A first analysis model was considering in 2D analysis slices of interest previously selected by a neurologist by analysing DWI sequence. A first CV process was carried out under the following conditions: input data included the following five contrasts DWI b0 and b1000, ADC, FLAIR and T2*. A second CV process integrated in addition clinical data. These clinical data were age, baseline NIHSS, high blood pressure history, diabetes mellitus history, atrial fibrillation history, onset-to-treatment time, anti-thrombotic treatment in progress. As Time-Of-Flight (TOF) could not be integrated to the input data, due to a too large difference in the field-of-view acquired as compare to the other MR sequences, an additional parameter has been included in the clinical data: the presence or absence of LVO.

A second analysis model was considering overall slices using a 2D analysis slice by slice. Two CV process was carried out as described above, with and without clinical data.

2.5. Statistical analysis

Categorical data were analysed in contingency tables using the χ^2 statistic to assess significance. Continuous data were compared using a student t-test when normality was assessed by Shapiro-Wilk test, using a Wilcoxon nonparametric test when it was not. P-value < 0.05 was considered significant. Multivariate analysis was performed considering significant variables with $p < 0.2$ in univariate analysis and relevant variables. Sensitivity and specificity of DWI-ASPECTS and THRIVE score were calculated regarding relevant cut-off value.

Accuracy was calculated for ML algorithm. Receiver Operating Characteristic (ROC) curves were built and their respective Area Under ROC curve (AUC) were calculated to assess DWI-ASPECTS, THRIVE score and ML algorithm performance. SPSS version 26.0 was used for all statistical analysis.

3. RESULTS

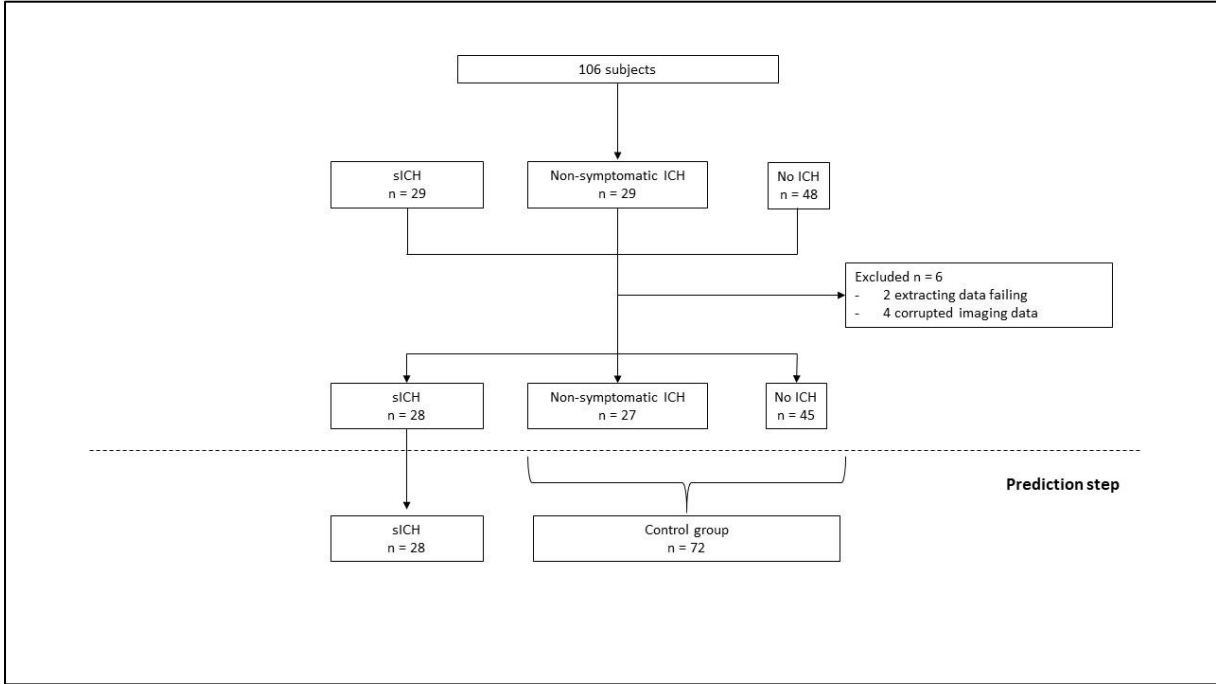


Figure 4: Flow Chart

3.1. Baseline characteristics

A total of 106 patients satisfied inclusion criteria. Four subjects were excluded because imaging data were corrupted. Two patients were excluded due to imaging data extraction fail.

Our cohort was then composed of 100 subjects: 28 in sICH group, 27 in non-symptomatic ICH group, 45 in no ICH group (Figure 4).

Distribution of baseline demographic characteristics, comorbidities and radiological findings, acute treatment undertaken and main outcomes between patients along the 3 groups are shown

in Table 1. Regarding acute treatment undertaken, 53 patients underwent only IVT, 9 patients underwent only MT and, 38 patients underwent a bridging therapy.

	sICH n = 28	Non-symptomatic ICH n = 27	No ICH n = 45
Age, mean ± sd	75.2 ± 14.5	72.4 ± 12.1	71.04 ± 14.2
Sex, n (%)			
Female	15 (54%)	10 (37%)	22 (49%)
Male	13 (46%)	17 (63%)	23 (51%)
Right sided stroke	12 (43%)	18 (67%)	28 (62%)
Treatment, n (%)			
IVT	16 (57%)	13 (48%)	24 (53%)
MT	5 (18%)	1 (4%)	3 (7%)
Bridging	7 (25%)	13 (48%)	18 (40%)
Clinical data			
NIHSS, median [IQ]	17 [13-21.3]	16 [14-17.5]	15 [13-17]
OTT, mean ± sd	199.3 ± 46.5	171.8 ± 44.2	172.97 ± 59.2
HBP, n (%)	20 (71.4%)	12 (44.4%)	28 (59.6%)
AF, n (%)	10 (35.7%)	11 (40.7%)	12 (26.7%)
DM, n (%)	9 (32.1%)	2 (7.4%)	10 (21.3%)
Antithrombotic, n (%)	19 (67.9%)	8 (29.6%)	13 (28.9%)
Imaging data			
DWI ASPECTS, median [IQ]	7 [5.75-8]	7 [6-8]	8 [7-9]
LVO, n (%)	22 (78%)	23 (85%)	36 (80%)
Clinical and radiological outcomes			
PH1	6 (21.4%)	0	-
PH2	16 (57.2%)	3 (11.2%)	-
HI	6 (21.4%)	24 (88.8%)	-
Functional independence, n (%)	0	12 (44.4%)	28 (62.2%)
In-hospital mortality, n (%)	15 (53%)	2 (7.4%)	1 (2%)

Table 1: Baseline characteristics according to each sample – IVT: Intravenous thrombolysis ; MT : mechanical thrombectomy; NIHSS : National Institutes of Health Stroke Scale; OTT : Onset-to-Treatment Time; HBP : High Blood Pressure history; AF : Atrial Fibrillation; DM : Diabetes Mellitus; LVO : Large Vessel Occlusion; mRS : modified Rankin Scale

3.2. Radiological and Clinical outcomes

Radiological and clinical outcomes between sICH and non-symptomatic ICH subjects are summarized in Table 2. In-hospital mortality was significantly higher in sICH subjects ($p < 0.001$). On the contrary functional independence at discharge was significantly less frequent in sICH subjects ($p < 0.05$). Rate of PH 1 and 2 were significantly higher in sICH group compared to non-symptomatics ($p < 0.001$). Functional outcomes remained significantly poorer in sICH group compared to control group with a lower rate of functional independence (0% vs 44.4%, $p < 0.005$) and a higher in-hospital mortality rate (53% vs 4.1%, $p < 0.005$) as shown in Table 3. Figure 5 illustrates Rankin at discharge's distribution according to group.

Radiological and clinical outcomes	sICH	Non-symptomatic ICH	P-value
Functional independence at discharge, n (%)	0	12 (44.4%)	$P < 0.05$
In-hospital mortality, n (%)	15 (53%)	2 (7.4%)	$P < 0.001$
PH1, n (%)	6 (21.4%)	0	$P < 0.001$
PH2, n (%)	16 (57.2%)	3 (11.2%)	
HI, n (%)	6 (21.4%)	24 (88.8%)	

Table 2: Radiological and clinical outcomes regarding sICH and non-symptomatic ICH subjects.

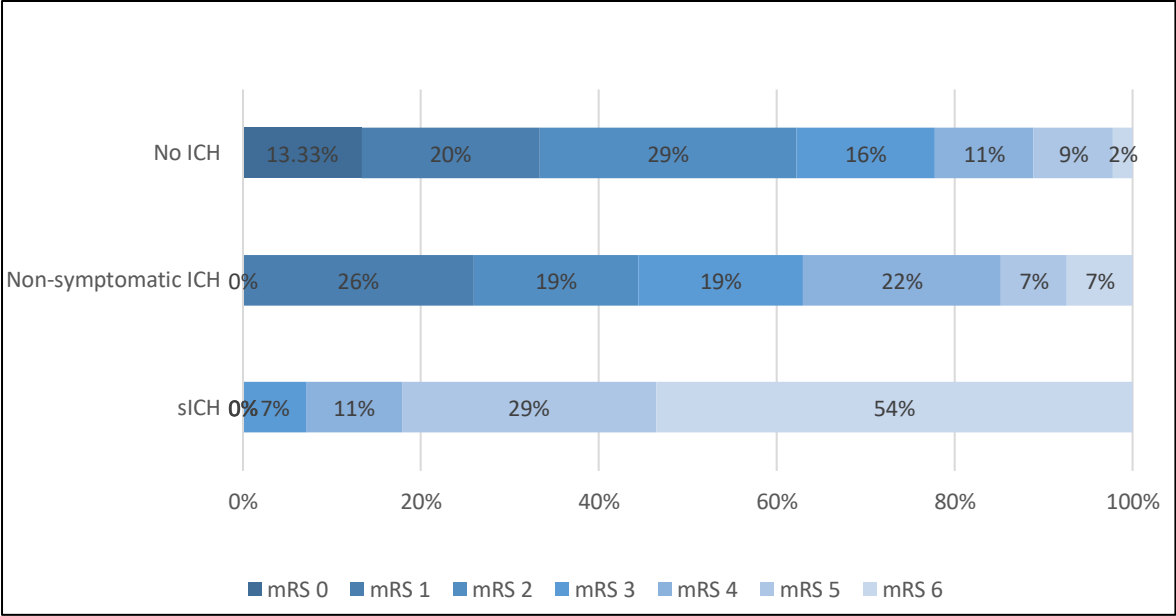


Figure 5: Modified Rankin scale (mRS) at discharge according to radiological features

3.3. sICH characteristics: univariate and multivariate analyses

Table 3 summarizes univariate analyses between sICH and control groups and main results of the multivariate model built afterwards. Baseline demographic characteristics were similar in age and sex. Type of treatment undertaken did not differ significantly between both groups. A non-significant higher rate of left stroke can be noted in the sICH group. Stroke severity, according initial NIHSS score did not differ significantly (median NIHSS was 17 [13–21.3] in sICH group versus 15.5 [13-17] in control group, $p = 0.12$). Main comorbidities also did not differ between the two groups. There was higher rate of diabetes mellitus in sICH group without reaching significance compared control group (32.1% vs 15.3%, $p = 0.058$).

Onset-to-Treatment Time was significantly higher in sICH group (mean OTT was 199.3 ± 46.5 vs 172.3 ± 53.8 , OR = 1.01 [1.001 – 1.02], $p = 0.01$). Use of prior anti-thrombotic treatment was more frequent in sICH group (67.9% vs 29.2%, OR = 5.1 [2 – 13.2], $p < 0.005$).

Concerning baseline imaging data, DWI-ASPECTS was lower in sICH group (median DWI-ASPECTS was 7 [5.75–8] in sICH group versus 8 [6–9] in control group, OR = 0.78 [0.63 – 0.97], $p = 0.04$). LVO was found for 78% of patients in sICH and 82% in controls which did not differ significantly.

Results of multivariate model main are shown in Table 3. Briefly, only prior use of antithrombotic treatment remained a predictive factor of sICH with OR = 4.4 [1.5 – 13.2] ($p = 0.008$), as well a DWI-ASPECTS with OR = 0.73 [0.56 – 0.97], $p = 0.03$ and THRIVE score (OR = 5.14, CI 95% [1.7 – 15.6], $p = 0.004$). Baseline NIHSS, high blood pressure history, atrial fibrillation, diabetes mellitus history, OTT and large vessel occlusion did not differ significantly between both groups.

	Groups		Univariate analysis		Multivariate model	
	sICH n = 28	Controls n = 72	OR [95%]	p-value	OR [95%]	p-value
Age, mean ± sd	75.2 ± 14.5	71.5 ± 13.4	1.02 [0.98 – 1.06]	0.25	1.007 [0.95 – 1.05]	0.8
Sex, n (%)			0.69 [0.29 – 1.67]	0.41	-	-
Female	15 (54%)	32 (45%)				
Male	13 (46%)	40 (55%)				
Right sided stroke	12 (43%)	46 (64%)	2.36 [0.96 – 5.74]	0.056	-	-
Treatment, n (%)			-	0.073	-	-
IVT	16 (57%)	37 (51%)				
MT	5 (18%)	4 (6%)				
Bridging	7 (25%)	31 (43%)				
Clinical data						
NIHSS, median [IQ]	17 [13–21.3]	15.5 [13-17]	1.09 [0.98 – 1.2]	0.12	1.07 [0.94 – 1.21]	0.27
OTT, mean ± sd	199.3 ± 46.5	172.3 ± 53.8	1.01 [1.001 – 1.02]	0.01	1.009 [0.99 – 1.02]	0.1
HBP, n (%)	20 (71.4%)	38 (52.8%)	2.2 [0.9 – 5.7]	0.09	1.04 [0.26 – 4.09]	0.95
AF, n (%)	10 (35.7%)	23 (31.9%)	1.18 [0.47 – 2.96]	0.7	0.98 [0.29 – 3.21]	0.97
DM, n (%)	9 (32.1%)	11 (15.3%)	2.63 [0.9 – 7.3]	0.058	1.82 [0.52 – 6.35]	0.34
Antithrombotic, n (%)	19 (67.9%)	21 (29.2%)	5.1 [2 – 13.2]	< 0.005	4.4 [1.5 – 13.2]	0.008
THRIVE score, median [IQ]	5 [4-6]	4 [3-5]	1.54 [1.15 – 2.07]	0.004	5.14 [1.7 – 15.6]	0.004
Imaging data						
DWI ASPECTS, median [IQ]	7 [5.75–8]	8 [6–9]	0.78 [0.63 – 0.97]	0.04	0.73 [0.56 – 0.97]	0.03
LVO, n (%)	22 (78%)	59 (82%)	0.8 [0.27 – 2.39]	0.69	0.33 [0.08 – 1.36]	0.12
Clinical outcomes						
Functional independence, n (%)	0	40 (56%)	-	< 0.005	-	-
In-hospital mortality, n (%)	15 (53%)	3 (4.1%)	-	< 0.005	-	-

Table 3: Baseline characteristics and outcomes between sICH subjects and control group, uni and multivariate analyses. Abbreviations are detailed in Table 1

3.4. Symptomatic intracranial haemorrhage prediction

3.4.1. THRIVE score performance

THRIVE score was significantly higher in the sICH group (OR = 1.54, CI 95% [1.15 – 2.07], $p = 0.004$) and remained an independent predictor of sICH in multivariate analysis (OR = 5.14, CI 95% [1.7 – 15.6], $p = 0.004$).

THRIVE score performance is represented by the ROC curve in Figure 6, with AUC of 0.664 (CI 95% [0.548 – 0.781]). Table 4 indicates Sensitivity/Specificity values, Positive Predictive and Negative Predictive Values (PPV/NPV) for each cutpoint. We can notice that a threshold of 4 gave an excellent sensitivity of 92.8% but a poor specificity of 40.2% for an overall 55% accuracy. Raising the threshold to 5 improved specificity to 55.5% but at the expense of a poor sensitivity of 60.7% for an overall 57% accuracy.

3.4.2. DWI-ASPECTS performance

DWI-ASPECT score was an independent factor of sICH in multivariate analysis (OR = 0.73 CI 95% [0.56 – 0.97], $p = 0.03$). DWI-ASPECT score predicted sICH with an AUC of 0.634 (CI 95% [0.508 – 0.761]). Table 4 indicates Sensitivity/Specificity values, Positive Predictive and Negative Predictive Values (PPV/NPV) for interest cutpoints. We can notice that setting a threshold of 7 - which is the most commonly used threshold in the literature- resulted in poor sensitivity and specificity calculated at 60.7% and 61.1% respectively which corresponds to 61% accuracy. ROC curve of DWI-ASPECTS is presented in Figure 6.

	Cutpoint	Se (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC
THRIVE SCORE	4	92.86%	40.28%	37.68%	93.55%	55%	0.664
	5	60.71%	55.56%	34.69%	78.43%	57%	
DWI-ASPECTS	7	60.71%	61.11%	37.78%	80%	61%	0.634
	8	82.14%	36.11%	33.33%	83.87%	49%	

Table 4: THRIVE score and DWI-ASPECTS sICH prediction: Sensitivity (Se), Specificity (Sp), Positive (PPV) and Negative (NPV) Predictive values according to relevant cutpoints.

3.4.3. Machine Learning (ML) algorithm

“Resnet” neural network performances were assessed in various configurations. Enlarging number of layers which, for reminder, increases the number of parameters taken into account and therefore the complexity of the network, did not improve performances. The network was finally made up of 15 convolutional layers preceding a single fully connected layer. Various data augmentation methods were used such as Gaussian blur effect, x-axis filing flip, contrast variation via the gamma function. None of these methods resulted in a significant improvement in performance.

According to each imaging dataset model, including either overall slices (all brain model) or pre-selected slices of interest (masked brain model), best results after learning phase and on validation dataset are listed below.

The best performance was achieved using the masked brain model computing the 5 contrasts and clinical data inputs (accuracy 77%). Without clinical data accuracy was 74%.

“All brain” model with clinical data achieved similar accuracy performances with best accuracy calculated at 74% compared 72% without clinical data inputs.

ROC curve and AUC for all brain and masked brain models including clinical data are illustrated in Figure 6. AUC were estimated at 0.624 (CI 95% [0.497 - 0.752]) and 0.658 (CI 95% [0.534 - 0.783]) respectively.

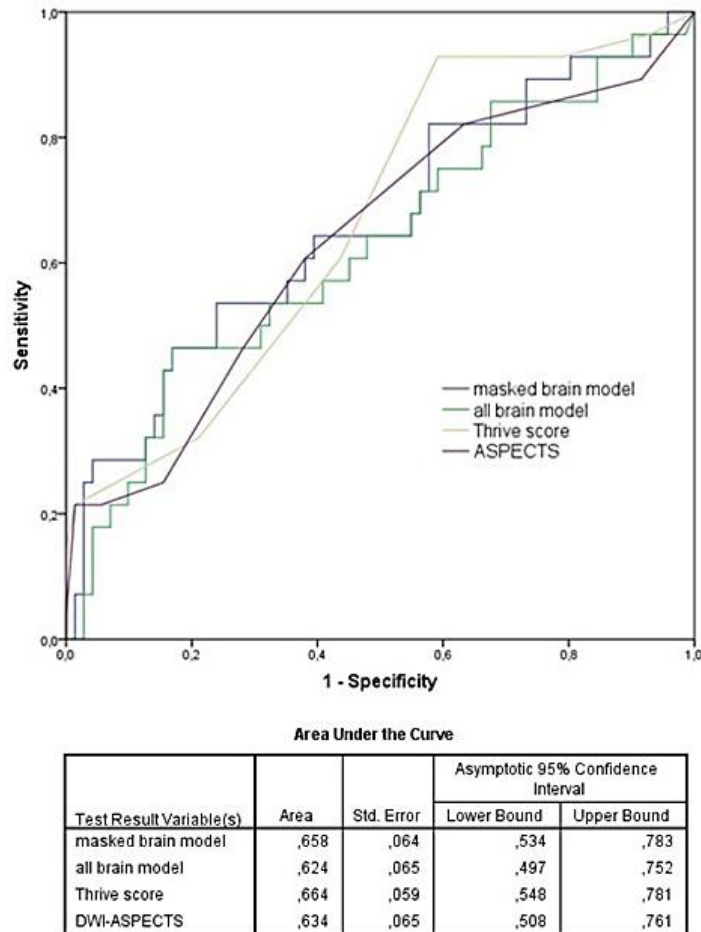


Figure 6: Receiver operating curves (ROC) and Area Under ROC Curves (AUC) of DWI-ASPECT SCORE (purple), THRIVE score (beige), artificial neural network (ANN) masked brain (blue) and ANN all brain (green) models.

4. Discussion

4.1. sICH outcomes

First of all, this study highlighted, in a population of anterior circulation AIS subjects matched on clinical severity and age, a number of clinical and radiological differences in patients with sICH.

Demographic data or reperfusion strategies did not differ significantly between sICH subjects and controls. More surprisingly, cardiovascular co-morbidities and risk factors were not significantly more present in the sICH group.

Only prior use of anti-thrombotic agent appeared as a predictive factor of sICH in multivariate analysis, which was consistent with literature (18). OTT, known as risk factor of sICH (17), was significantly longer in sICH group in univariate analysis but not in multivariate model.

Regarding imaging baseline parameters, DWI-ASPECTS was significantly lower in the sICH group. This argues in favour of a higher lesions volume in the sICH group and is also consistent with data available in the literature (32). Although some authors have linked signs of proximal occlusion and especially spontaneous hyperdensity of the middle cerebral artery on CT scan (20), LVO rate was not significantly higher in sICH subjects inside our cohort. Thus, these results raises the hypothesis that infarcted tissue volume may be more relevant than hypoperfusion volume to predict sICH, although these two parameters have been related to poor outcome (45).

Functional outcomes and survival rate were poorer in sICH group compared to the reference group but also, more specifically, compared to non-symptomatic ICH patients, strengthens the importance of identifying patients at risk of sICH. From a radiological point of view, we noticed a significantly higher rate of PH within sICH subjects compared to the reference group but also compared to ICH patients. This underlines the probable link between the type of haemorrhagic

transformation and its severity, as suggested by other authors : post hoc analysis of ECASS I and II data demonstrated an increased risk of early neurological deterioration and 3-month mortality after PH2-related ICH (13,17), describing close to a 50% mortality with PH2. Future work could therefore specifically focus on the identification of PH2 predictive factors rather than sICH. The analysis of the initial imaging, including using ML methods as presented here, could be particularly relevant in this case.

4.2. Predictive performances

Secondly, this work highlighted difficulties for current tools to predict sICH.

The THRIVE score showed in our cohort moderate performance in predicting sICH. It was significantly higher in the sICH group and remained an independent predictor of symptomatic haemorrhagic transformation in multivariate analysis. Nevertheless, in detail, its performance on a ROC curve remained modest with AUC estimated 0.664. Applying a decision-making threshold of 4 allowed to obtain an excellent sensitivity of 92.8% but a poor specificity of 40.2%. These results were similar to other authors (30) and probably explain why this score is not used in routine practice.

DWI-ASPECT score also showed poor performance to predict sICH in our cohort. It was significantly higher in the sICH group and remained an independent predictor of sICH in multivariate analysis. Nevertheless, performances remained modest with AUC estimated 0.634. Sensitivity and specificity were 61% for both with a 7 points cut-off which is current threshold used in current practice. Setting a 8 points cut-off allows to get close to other authors results (32) and resulted in an interesting 82% Sensitivity but once again at the expense of a poor 33% specificity. To discuss these poor DWI-ASPECTS results, we should remember that ASPECTS was originally assessed on CT scan and so based on hypoattenuation signs (19). This hypodensity in CT scan appears more latter than DWI hyperintensity, and therefore reflects

greater substance changes in infarcted tissue and a greater progression towards necrosis. Thus, the ASPECTS on CT scan was probably more specific of a tissue at risk of haemorrhage. Moreover, DWI-ASPECT is a good estimation of lesion volume, but some limits are recurrently noted: lesion location is not considered and lesion volume could be more reliably quantified on DWI maps nowadays (46). In addition, this global estimate of lesion volume, unlike an automated analysis, does not take into account differences in the intensity of the DWI signal and ADC, even though this parameter could be an indicator of the degree of ischaemia and has been linked to the risk of sICH (21,47).

Concerning ML algorithm performances, this study showed that in a cohort of patients matched on clinical severity and age, an MRI based ML algorithm was able to discriminate subjects at risk of sICH. Best accuracy of 77% was reached with a model focused on slices of interest only including ischemic parenchyma and including clinical data. Interestingly, removing clinical data from the inputs did not significantly affect the algorithm performance (accuracy 74%). This finding seems consistent with the absence of significant differences between groups for these parameters and points to other possibilities that we will discuss below. Surprisingly, performances of “all brain” model were similar to the “masked brain” model. From a conceptual point of view, we expected that this model would not work properly in a 2D analysis, as independent slices of unaffected parenchyma to be labelled sICH or control group. This could be explained by the presence of predictive elements in unaffected parenchyma (i.e., FLAIR intensities or microbleeds burden as described above). Nevertheless, in detail, building ROC curves revealed AUC estimated at 0.624 and 0.658 which do not outperform DWI-ASPECT and THRIVE scores.

To sum up, we have attempted a new approach using a machine learning algorithm capable of synthesizing the diversity of data that seem necessary for sICH prediction. This study brings novel contributions to sICH prediction in that it was designed to develop a ML method usable in current practice by clinicians to predict sICH. As a result, we chose to use standard practice MRI data computed using different MRI equipment and we decided to implement data available before introduction of reperfusion therapies. We proved that ML algorithm was able to process the diversity of information provided to achieve sICH prediction. Nevertheless, ML algorithm's predictive performances did not outperform current tools. These poor performances and, moreover, the importance of pre-processing, which requires the selection of interesting slices by the investigator, do not make it a tool that can be routinely used to date. These modest but encouraging results open up a number of avenues for development.

4.3. Study limitations and future directions

The above-mentioned choices led to certain limitations.

First, to be as close as possible to current practice we included all treated patients whatever the treatment introduced. But this has consequently increased the heterogeneity of a cohort which is also small in size, in particular because some patients did not receive IVT.

Then, clinical data used here may not be the most relevant ones, as highlighted by the fact that they little differed in sICH subjects. This leads us to look for more relevant input clinical data. Baseline mean blood pressure and glycaemia are missing, while those factors are more strongly correlated to sICH risk than HBP and diabetes mellitus history (48,49). In order to be useful in current practice, it would also seem more relevant to consider the Onset-to-Imaging Time rather than OTT which cannot be estimated *a priori*, especially in case of MT without prior IVT.

MRI data seemed to be particularly relevant since we can already see a discriminating power of the algorithm mainly based on these imaging data. We can discuss the choice of MR

sequences as input data. In this work, the absence of perfusion sequence or at least a TOF sequence that might have provided information on collaterality can be highlighted. Perfusion sequences were not usually performed in most of stroke centres. However, permeability imaging, which consists of delayed acquisition perfusion imaging assessing late extravasation into the brain parenchyma, has been identified as predictor of sICH in that it requires the blood-brain barrier to be sufficiently disrupted to allow entry of gadolinium (42). Blood brain barrier disruption is a critical element involved in the development of haemorrhagic transformation (50) and could be identified by MRI on gadolinium enhanced-T1-weighted sequences (51). Perfusion imaging currently has no place in stroke emergency imaging. However, in this field too, certain ML techniques could bring new contributions, by reconstructing fully injected sequences after a low-dose injection or recovering permeability parameters from a single brief acquisition using fingerprinting methods (52,53). TOF sequence failed to be integrated for technical reasons because of differences in acquisition volume. However it has been suggested that the presence of a robust collateral circulation on vessel imaging is associated with a lower risk of ICH, which may be partly due not only to the smaller volume of the infarction but also to the collateral circulation, ensuring sufficient circulation for the cerebral endothelial cells so that they do not rupture as a result of prolonged ischemia (54).

Then, the small size of the cohort may be the most important limitation. Indeed, ML methods require a large amount of data to improve learning phase. Due to the small workforce, particular attention had to be paid to the risk of overfitting. Overfitting occurs when the algorithm, through repeated training, finally recognises the training dataset. We then observe excellent performance on the learning data but paradoxically poor performance on the validation set. This risk of "overlearning" increases in inverse proportion to the cohort size. This led us to limit the learning phase.

As a result, this lack of data led us to focus on a 2D analysis which had the advantage of artificially increasing cohort size. Each patient gave rise to a certain number of cuts which could be analysed independently during the training phase. However, this strategy most certainly led to the loss of a lot of relevant information to prediction. The advantage of “all brain” model was to benefit from all the information provided by the parenchyma both inside and outside the lesion, it may consider visible leukopathy in FLAIR (23,55) and microbleeds burden visible on T2* sequence which has also been correlated with sICH risk by some authors (24). But the interpretation of non-affected and non-informative parenchyma slices may have reduced its performance. On the contrary, “slices of interest” model was supposed to get around this difficulty of 2D analysis but at the expense of a loss of information. The 2D analysis also meant that neither of the two models could accurately calculate the lesion volume, although this data seems to be a key factor (25). It has been reported that patients with large lesions on DWI-MRI and Perfusion Weighted MRI have a high risk of developing sICH and a worse clinical outcome after intravenous thrombolysis (47). The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study identified a threshold of ≥ 100 -mL lesion volume in DWI sequence (45), characterizing a malignant course. Moreover, little access to the location of the lesion within the brain was allowed using this 2D analysis, which could be essential to assess the symptomatic nature of the haemorrhage.

Finally, increasing dataset seems therefore to be a first necessary condition to further works. A larger dataset would allow 3D analysis, avoiding a selection of interest slices that results in the loss of valuable information such as lesion volume and unaffected parenchyma characteristics. Enlarging dataset through a prospective work would also be an opportunity to collect more relevant clinical and radiological inputs. Moreover, validation of these results on a more heterogeneous external population is also required.

5. Conclusion

THÈSE SOUTENUE PAR : Florent LEPILLIET

TITRE:

PREDICTING SYMPTOMATIC INTRACRANIAL HAEMORRHAGE IN ACUTE ISCHEMIC STROKE: INTRODUCTION TO A CLINICAL-RADIOLOGICAL AND MRI-BASED MACHINE LEARNING APPROACH

Ischemic stroke is a leading cause of death and disability in adult. Reperfusion therapies using intravenous thrombolysis (IVT) and endovascular interventions such as mechanical thrombectomy (MT) improve functional outcomes in patients with acute ischemic stroke (AIS) but unfortunately, these therapeutics increase the risk of intracranial haemorrhage (ICH) of ischemic brain tissue. Several definitions and classifications exist to define this complication, on a clinical or radiological level. However, high evidence indicates that symptomatic ICH (sICH) is the most relevant definition as it is most correlated with poor outcome. Several methods, based on clinical and/or radiological data, failed to predict the risk of haemorrhagic transformation in clinical practice.

We attempted a new approach by training a supervised machine learning (ML) algorithm on clinical and MRI data within a 100 subjects cohort of patients with anterior circulation AIS treated by IVT and/or MT who underwent sICH (n=28), non-symptomatic ICH (n=27) and 45 controls with no bleeding, matched on clinical severity and age. We compared ML algorithm accuracy to the performance of the clinical Total Health Risks in Vascular Events (THRIVE) score and to the radiological Alberta Stroke Program Early CT Score applied to MR imaging (DWI-ASPECTS).

ML algorithm predicted sICH with an Area Under receiver operating characteristic Curve (AUC) of 0.658 (CI 95% [0.534 – 0.783]). Applied in the cohort, estimated AUC of THRIVE

score and DWI-ASPECTS were 0.664 (CI 95% [0.548 – 0.781]) and 0.634 (IC 95% [0.508 – 0.761]), respectively. Nevertheless, this work showed that this algorithm was able to synthesize all clinical and radiological data provided and integrating the variety of information provided by MR imaging to provide a probability of sICH.

Further studies are needed to improve these performances. Enlarging dataset is needed to improve learning phase, reduce overfitting risk and allow a 3D analysis to avoid data loss. More relevant clinical and radiological data could also be integrated to improve performances. Validation of these results on a more heterogeneous external population is also required.

VU ET PERMIS D'IMPRIMER
Grenoble, le : 8/02/21

LE DOYEN


Pr. Patrice MORAND
pour le conseil
et par délégation
—
Le Doyen de Médecine
Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE

Pr. Olivier DETANTE



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Le serment d'Hippocrate

Texte revu par l'Ordre des médecins en 2012

“

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je

sois déshonoré(e) et méprisé(e) si j'y manque. ”