Using ANFIS to Predict the Long and Short Term Stroke Risk Based on Ultrasound Carotid Imaging and Clinical data of Initially Asymptomatic Patients

Received 29 January 2023; Accepted: 22 February 2023 *Research Article*

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***Abstract*—The aim of this study is to investigate the development of predictive modelling in order to estimate the short (less or equal to three years) or long term (more than three years) stroke risk of patients with asymptomatic carotid artery stenosis. Data were collected from 108 patients that had a stroke event have been used. The prediction is done using base line data where patients were still asymptomatic. The information collected includes non-invasive ultrasound images of the carotid arteries and several other clinical data like patient's blood tests (Cholesterol, creatinine, general blood parameters), diabetes, smoking, family history. Ultrasound images were analyzed and several features that can be used in order to characterize the type, size, structure and morphology of the atherosclerotic plaques where extracted. Based on the extracted image features and clinical data; we had created a risk modelling system based on Adaptive Network based Fuzzy Inference System (ANFIS). Model was investigated to classify the subjects into the two classes i) short (≤3 years) and ii) long term (>3 years) period stroke events. The ANFIS could give us correct classification rate up to 97±2.6%. These results can clearly indicate that ultrasound image plaque characteristics in combination with clinical data can be used in order to create predictive models for stroke risk period.**

Keywords— Adaptive Network based Fuzzy Inference System (ANFIS), stroke risk, Feature Selection.

I. INTRODUCTION

Atherosclerosis of the internal carotid artery (ICA) is an important risk factor for stroke. Using the NASCET method [1] for the determination of stenosis the risk of stroke has been shown to range between 0.1-1.6% per year for asymptomatic individuals with ICA stenosis <75-80%. The risk rises to 2-3% per year for individuals with higher grades of stenosis [2][9]. In the past three decades carotid endarterectomy was extensively used for the reduction of stroke risk. This is because two randomized controlled trials, almost a decade apart, the ACAS in 1995 [3]and the ACST in 2004 [4] reported that in patients with asymptomatic ICA stenosis >60-70% (using the NASCET method) carotid endarterectomy reduced the risk of stroke from 2% to 1% per year [4], [5]. However, in these trials carotid endarterectomy was associated with a 2-3% perioperative rate of stroke or death making it marginally effective for asymptomatic patients. It should also be noted that in these trials, medical therapy, which was left to the discretion of the local teams, was suboptimal in relation to current practice. Recent advances in the management of vascular disease and particularly the use of statins appear to have reduced stroke rate to approximately 1% per year and have prompted doubt regarding the value of endarterectomy in asymptomatic patients [6], [7], [9]. In addition, medical therapy was found to be 3 to 8 times more cost effective than surgical [8], [9]. However, we believe that carotid endarterectomy can still be justified if subgroups at increased risk can be identified. This raises the need for the establishment of methods for reliable and objective cerebrovascular risk prediction and stratification [9].

Non-invasive ultrasound imaging provides information not only on the degree of carotid artery stenosis but also on the characteristics of the arterial wall including the size and consistency of atherosclerotic plaques [10]. Carotid stenosis alone has limitations in predicting risk and does not show plaque vulnerability and instability, thus other ultrasonographic plaque morphologic characteristics have been studied for better prediction of risk stroke. Plaque echogenicity as assessed by B-mode ultrasound has been found to reliably predict the content of soft tissue and the amount of calcification in carotid plaques.

Additionally, it has been reported that subjects with echo lucent atherosclerotic plaques have increased risk of, ischemic cerebrovascular events [10]. Most recently [11], [12], [16] showed that plaque echo lucency can be used to predict stroke. Other studies have reported that plaques that are more echo lucent and heterogeneous are often associated with higher cerebrovascular risk and the development of ipsilateral neurological symptoms [13], [14]. In contrast, homogeneous hypoechoic and hyperechoic plaques without evidence of ulceration usually remain asymptomatic.

Prediction of risk is important, as it will aid clinicians in the selection of asymptomatic cases at higher risk. Equally important is the establishment of a method that will allow evaluation of objective, quantitative and urgency of high-risk cases. These results will help identify the ones that would most benefit from endarterectomy. This paper aims towards the development of predictive modeling to identify group of patients that are at high risk of stroke in a short-term period (≤ 3 years) as opposed to group of patients that are at a high risk of stroke in long term (> 3 years). This threshold was selected based on the initial statistical analysis of the data set collected from a multicenter cohort study called Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) [2]. Several image analyses as well as clinical features were extracted from the patients.

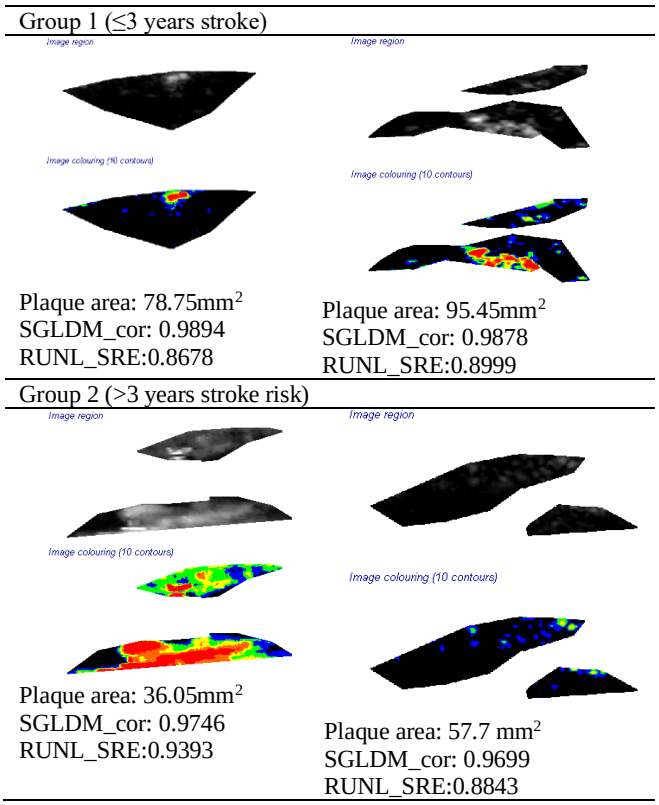

Fig. 1. Example of selected plaques at baseline, using b-mode ultrasound images and colour contoured plaques with selected

TABLE I. NUMBER OF ASYMPTOMATIC AND STROKE (INCLUDING TIA'S) CASES, SEPARATED INTO SUBGROUPS ACCORDING TO ECST STENOSIS AND NASCET STENOSIS. FOLLOW-UP 6 MONTHS TO 8 YEARS (MEAN, 48 MONTHS) [2]. GROUPS OF YEARS OF EVENT ARE FOR ≤3 YEARS GROUP ONE AND >3 YEARS GROUP TWO.

ECST st(%)	NASCET st(%)	No.	Asymp.	Stroke	Group 1/2
All		1121	991(88.4%)	108(9.6%)	65 / 27
50-69	<50	198	182(92%)	12(6.1%)	13 / 5
70-89	50-82	598	533(89.1%)	56(9.4%)	28 / 11
90-99	83-99	325	276(84.9%)	40(12.3%)	24 / 11

TIAs, transient ischemic attacks;
ECST, European Carotid Surgery Trial;
NASCET, North American Symptomatic Carotid Endarter. Trial

Images were initially statistically analyzed in order to identify if there is significant difference between the two groups and get an initial statistical model for classification of the two groups. Adaptive Network based Fuzzy Inference System (ANFIS) was used in order to create a model for automated classification of patients at long- or short-term stroke risk. The work is based on initial work published by the group in [15] .

II. METHODS

A. Patient recruitment

Data used in this study were collected through the Asymptomatic Carotid Stenosis and Risk of Stroke study. Patients included in the study should be newly referred (< 3 months), with 50-99% ICA stenosis in relation to the carotid bulb diameter (ECST method) without previous ipsilateral cerebral or retinal ischemic (CORI) symptoms and without neurological abnormalities. They were recruited to the study after written informed consent. Patients who had had contralateral cerebral hemispheric/retinal or vertebrobasilar symptoms or signs of stroke/ transient ischemic attack (TIA) were included if asymptomatic for at least 6 months prior to recruitment. For patients with bilateral carotid atherosclerosis the side with the more severe stenosis was considered ipsilateral (the study artery) [2].

Data were collected at baseline when all patients were still asymptomatic; The data included duplex ultrasound scanning of the carotids. This was a procedure repeated at 6 months intervals until a primary endpoint or the end of the study was reached [2]. Duplex ultrasound scanning data were performed using a protocol and standard procedure specified during the study. These included artery stenosis and plaque characteristics based on image analysis algorithms. In addition to imaging several clinical data were collected. These included parameters like total cholesterol, LDL cholesterol, HDL cholesterol, Creatinine, Triglycerides etc. as published in [2][16].

TABLE II. MEAN, STANDARD DEVIATION AND PARAMETRIC TEST OF EQUALITY OF MEANS (SIG.) FOR THE THREE FEATURE SETS INVESTIGATED STROKE GROUPS: (1) ≤ 3 YEARS OF EVENT AND (2) > 3 YEARS OF EVENT.

Group	Group 1	Group 2	Sig.
Feature Set 1 (FS1) Clinical and Plaque Feat. [2][16]			
Sten(%ECST)	81.97±11.17	80.33±13.75	0.552
Log(GSM+40)	4.026±0.235	4.098±0.234	0.186
(Plq Area)$^{1/3}$	3.936±0.758	4.172±0.647	0.159
DWAs	0.785±0.414	0.889±0.320	0.245
Hist TIA/Stroke	0.292±0.458	0.444±0.506	0.163
Feature Set 2 (FS2) Texture Feat. SGLDM [2][16]			
ASM	0.077±0.126	0.040±0.065	0.159
CON	57.23±62.33	45.02±29.34	0.334
COR	**0.972**±0.019	**0.981**±0.007	**0.028**
VAR	1089±820	1353±977	0.188
SAV	57.65±30.18	68.65±34.60	0.131
SVA	4300±3247	5367±3885	0.180
SEN	4.437±0.985	4.77±0.658	0.111
ENT	6.10±1.49	6.60±0.981	0.107
DVA	36.79±42.66	27.21±18.78	0.266
DEN	2.26±0.504	2.38±0.290	0.228
InM1	-0.42±0.06	-0.41±0.03	0.342
InM2	0.97±0.03	0.98±0.01	0.131
Feature Set 3 (FS3) Textur Feat. Runl FPS [2][16]			
sqrrunl	133.28±35.56	113.06±37.58	0.017
runl_SRE	0.909±0.033	0.894±0.022	0.026
fps_frad	3320±1432	2611±1549	0.038
fps_fang	2906±1301	2278±1411	0.043
runl_LRE	2.045±0.678	2.343±0.392	0.036
Runl_RP	23.26±10.13	17.71±13.55	0.033
Feature Set 4 (FS4) Text Feat. Morphology [18]			
L img cdf 1	0.020±0.023	0.016±0.017	0.442
L img cdf 2	0.057±0.064	0.052±0.048	0.685
L img cdf 3	0.103±0.109	0.094±0.071	0.694
L img cdf 4	0.146±0.141	0.141±0.091	0.854
L img cdf 5	0.190±0.167	0.187±0.112	0.935
L img pdf 1	0.020±0.023	0.016±0.017	0.442
L img pdf 2	0.037±0.042	0.035±0.032	0.842
L img pdf 3	0.046±0.046	0.042±0.027	0.725
L img pdf 4	0.043±0.034	0.046±0.026	0.628
L img pdf 5	0.044±0.033	0.046±0.029	0.727

* SIGNIFICANTLY DIFFERENT MEANS (P < 0.05) WITH PARAMETRIC TEST FOR TWO INDEPENDENT SAMPLES

The total number of patients collected through the study was 1121 out of which 108 strokes or TIAs were recorded. The characteristics of the different groups are shown in Table I. In the present study we had used data from subject that had Stroke and TIA events. These were further divided into two groups of patients, those that had an event in ≤ 3 years from baseline called short term group (group 1) and those that had an event in > 3 years from baseline called long term group (group 2).

B. Feature sets:

The feature sets extracted using image analysis as well as the clinical data sets were used in order to create and test the classification model. The image analysis features were also presented in previous studies [16], [17] and used for the classification of asymptomatic versus symptomatic patients.

Image analysis features were computed using the "Plaque Texture Analysis software" by LifeQ medical (http://www.lifeqmedical.com/).The standardization of images was done using an image normalization protocol as documented in [2][17].

The image analysis algorithms used for this study namely were the:

1) Statistical Features (SF) [2], [16] (see Table II, Feature Set1 - FS1). Stenosis based on ECST, logarithmic value of Gray Scale Media plus forty (log(GSM+40)), cubic root of the total plaque area (Plaque area)1/3 , presence of discrete white areas on plaques(DWA), history of contralateral TIA and/or Stroke.

2) Spatial Gray Level Dependence Matrices (SGLDM) features [16], [17] (see Table II, Feature Set 2 - FS2). Angular second moment (ASM), contrast (CON), correlation (COR), variance (VAR), sum average (SAV), sum variance (SVA), sum entropy (SEN), entropy (ENT), difference variance (DVA), difference entropy (DEN), information measures 1 & 2 (InM1, InM2).

3) Features based on Run Length Statistics Algorithm [16], [17]. (see Table II, Feature Set 3 – FS3) Short Run Emphasis (SRE), Long Run Emphasis (LRE), Run Percentage (RP). Fourier Power Spectrum Angular (Fang) and Radial (Frad) power.

4) Additionally, plaque multiscale morphology features were extracted as described in [18] (see Table II, Feature Set 4 – FS4). This method leads to the consideration of morphological features that come from: (i) dark regions associated with lipid, thrombus, blood, or haemorrhage, (ii) bright regions associated with collagen and calcified components, and (iii) medium-brightness regions that fall between them as discussed in [18]. The morphological probability density function (L-pdf) and the cumulative distribution function (L- cdf) for several radii of the structural element and for the low images created using a multiscale morphological decomposition, were calculated and used in this study.

C. Feature Selection:

Features used with SVM classifier were selected based on the statistical analysis and results presented in studies [16], [17]. While the features used with ANFIS were selected with the G-flip algorithm. G-flib algorithm is type of greedy search algorithm that depends on maximizing the evaluation function e(F), where F is a set of features. The algorithm repeatedly iterates over the feature set and updates the set of chosen features. In each iteration it is decided to remove or add the current feature to the selected set by evaluating the margin term in the equation 1 with and without this feature. The following equation shows the evaluating function for a training set S and a weight vector w according to the second definition of the margin in

$$e(w) = \sum_{x \in s} \Theta^{w}_{s/x}(x) \quad (1)$$

This algorithm converges to a local maximum of the evaluation function, as each step increases its value and the number of possible feature sets is finite. The computational complexity of one pass over all features of Gflip is

$$\Theta\left(N^2 m^2\right) \quad (2)$$

where N is the number of features and m is the number of instances. Empirically G-flip converges in a few iterations and there is no need to tune the number of features or any type of threshold [22].

D. Risk Modelling

Risk modeling was carried out using Adaptive Network based Fuzzy Inference System (ANFIS) [23]. The model was investigated to classify the patients into two classes: (i) short term stroke (≤ 3 years of event) and (ii) long term stroke (including TIA's) (> 3 years of event).

The ANFIS structure is composed of five layers and it [23] is demonstrated in Fig. 2. The first layer executes a fuzzification process, the second layer executes the fuzzy and the antecedent part of the fuzzy rules, the third layer normalizes the membership functions (MFs), the fourth layer executes the consequent part of the fuzzy rules and the fifth layer computes the output of the fuzzy system by summing up the outputs of the fourth layer.

The feed forward equations of ANFIS are as follows:

$$w_i = \mu_{A_i}(x) \times \mu_{B_i}(y), \quad i = 1,2 \quad (4)$$

$$\overline{w_i} = \frac{w_i}{w_1 + w_2}, \quad i = 1,2 \quad (5)$$

$$f = \frac{w_1 f_1 + w_2 f_2}{w_1 + w_2} = \overline{w_1} f_1 + \overline{w_2} f_2 \quad (6)$$

Where $f_1 = p_1 x + q_1 y + r_1 z,$

$$f_2 = p_2 x + q_2 y + r_2 z \quad (7)$$

In order to model complex nonlinear systems, the ANFIS model carries out input space partitioning that splits the input space into many local regions from which simple local models (linear functions or even adjustable coefficients) are employed. The ANFIS uses fuzzy MFs for splitting each input dimension. The input space is covered by MFs which are overlapping; that means several local regions can be activated simultaneously by a single input.

As simple local models are adopted in ANFIS model, the ANFIS approximation ability will depend on the resolution of the input space partitioning, which is determined by the number of MFs in ANFIS and the number of layers. Usually, MFs are used as bell-shaped with maximum equal to 1 and minimum equal to 0 such as [23].

ANFIS as Fuzzy Inference system the number of inputs must be avoid the curse of dimensionality situation. In such

situation the number of fuzzy rules increases exponentially with the number of inputs variable. To avoid the curse of dimensionality best features are selected by Greedy feature flip (G-flip) features selection algorithm.

III. Results

A group of 92 patients that had stroke or TIA were analyzed (16 patients were excluded due to missing clinical features (FS1)). Stroke patients consisted of two groups:

1. group 1 of 65 patients that had stroke =< 3 years from baseline, and
2. group 2 of 27 patients that had stroke > 3 years from baseline.

The following feature sets (FS) were computed for the two groups of stroke patients as given in Table II:

- FS 1: ACSRS Clinical and plaque features: stenosis (%ECST), log(GSM+40), (plaque area)$^{1/3}$, DWA absent or present, and history of contralateral TIAs and/or Stroke.
- FS 3: Texture Features – SGLDM: SGLDM Spatial Gray Level Dependence Matrices - ASM, CON, COR, VAR, SAV, SVA, SEN, ENT, DVA, DEN, InM1, InM2.
- FS 3: ACSRS additional texture features as concluded from the statistical analysis: Runl_SRE, Runl_RP, Runl_LRE, Fps_fang, Fps_frad.
- FS 4: Texture Features – Morphology: Low image cdf 1-5, and pdf 1-5.

IV. Discussion

Use of ultrasound imaging in defining stroke risk in asymptomatic patients has been presented through several studies [1], [2], [3], [5], [12], [13]. Despite the large number of publications, visual evaluation of plaques has several limitations and the acquisition procedure must be according to a predefined protocol in order to achieve the anticipated results **Hata! Başvuru kaynağı bulunamadı.**. Several r esearchers are currently discussing non-surgical interventions for reducing stroke risk and prevention of possible stroke events [7] - [9]. The ultrasonic appearance of carotid plaques was proved a good predictor for stroke events [3], [11]. Despite the simplicity of calculation features like the Gray Scale Median of a plaque [5] have shown high significance on the estimation of the risk of stroke. Additionally, features applied for vision analysis (texture or shape morphology) proved to give some extra information on the final estimation of stroke risk [12][16]. All the above conclude that the prediction of risk is important as it will aid clinicians in the selection of asymptomatic cases at higher risk. Equally important is the establishment of a method that will allow for objective and quantitative evaluation of high-risk cases, that are the ones that would most benefit from endarterectomy.

Despite all these and according to our knowledge no study presented asymptomatic patients risk estimation correlated with time period. Based on the statistical analysis of the data collected through the ACSRS study [2]; the effort of this work was on the development of predictive modeling to identify groups of patients that are at high risk of stroke in a short term period (≤ 3 years) as opposed to groups of patients that are at a high risk of stroke in long term (> 3 years). This threshold was selected based on the initial statistical analysis of the data. Estimation of short versus long term risk can give physicians time for medical intervention except from surgery. Several ultrasound image analysis features as well as clinical features. The statistical analysis showed that the significant difference was better supported from the same features used for stroke versus asymptomatic patients estimation [2][12][16]. Simple features like the Gray Scale Median, the area of the plaque, the presence of discrete white areas in the plaque [17] proved to give very good classification results. The combination with classical texture features like the SGLDM and morphological features was able to improve the overall performance at a percentage of 97% when using the ANFIS. The introduction of a classification model called Adaptive Network based Fuzzy Inference System (ANFIS) ended to a very promising result for this feature set. Based on these we can see that these features can be used as an indicator for the estimation stroke risk as long (more than 3years) or short time (less or equal than 3 years).

V. Conclusions:

For the first time we are showing that the stroke risk can be divided into groups of short-term groups, less or equal to three years and long term group, more than three years. The data used were collected from the ACSRS study where monitoring of the patients started when they were still asymptomatic and continued up to a period of 8 years. The predictive model is based on ANFIS classifiers. We had used several clinical feature sets recorded during the ACSRS study as well as features extracted from the images of the study. The results are very encouraging and they are consistent with results presented by the group and other researchers in previous studies that were dealing with the identification of asymptomatic versus symptomatic plaques. We anticipate that the combination of these results with analysis of data from real time ultrasound video could become a significant tool, which could support the decision AND URGENCY for carotid plaque surgery.

Contrubition Of The Authors

The contributions of the authors to the article are equal.

Conflict Of Interest

There is no conflict of interest between the authors.

TABLE III. Short term and long term stroke risk ANFIS predictive modelling evaluation results (computed based on 10 random sets of 40 patients each where the evaluation was carried out using leave one out method for each set). Features sets were used as tabulated in Table II.

FS1	FS2 – Selected	FS3	FS4	FS5 – Selected	Classifier	Correct classification	Sensitivity	Specificity
+					A	95.44±0.40	95.00±0.8	95.87±0.8
	+				A	96.58±0.92	95.00±1.85	98.15±1.85
		+			A	**97.43±2.57**	97.50±2.34	97.36±2.64
			+		A	92.44±7.56	92.94±8.05	91.95±8.05
				+	A	96.12±0.66	95.00±1.32	97.25±1.32

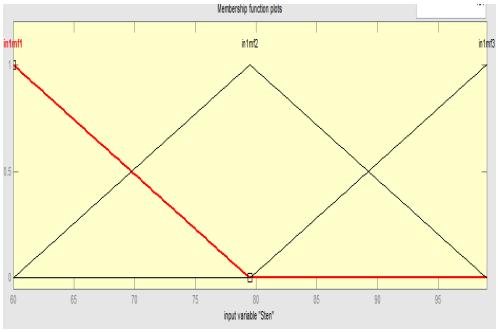

Fig. 2. Three Inputs member functions (MFs are generlaize trianglular by three parameters)

STATEMENT OF RESEARCH AND PUBLICATION ETHICS

Research and publication ethics were observed in this study

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