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DOMAIN
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CLINICAL AND IMAGING PROGNOSTIC FACTORS IN SPONTANEOUS CEREBRAL HEMORRHAGE

SUMMARY OF DOCTORAL THESIS

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1. Introduction

Stroke represents a major global health problem with an increasing socio-demographic burden in the past years. This increasing burden is a consequence of the epidemiologic aging of the population in the developed world and the epidemiologic shift towards an increasing prevalence of cardiovascular and cerebrovascular diseases in the developing world. This shift is explained by lifestyle improvement and the widespread adoption of an occidental way of living.

Hemorrhagic stroke represents approximately a quarter of all strokes, but the social impact of this pathology is a major one, due to very high rates of morbidity and mortality, which approach in absolute values the morbidity and mortality of ischemic strokes. Furthermore, the incidence of hemorrhagic stroke is increasing in developing countries which confront themselves with an increased prevalence of vascular risk factors and the lack of financial resources necessary to implement high-performance healthcare systems which can adopt primary prevention measures and offer high-tech hyperacute treatment at the highest standards.

The mortality rate of cerebral hemorrhage remained relatively stable during the past years being approximately 40% at 30 days.(1) This lack of improvement in the morbi-mortality rate of cerebral hemorrhage as opposed to the improvements observed in the morbi-mortality rate of ischemic stroke is linked to the lack of new efficient therapeutic measures that can improve the prognosis of these patients. The therapeutic options for patients suffering a cerebral hemorrhage have suffered minor changes during the past years, with many therapies that were initially considered promising being abandoned as a result of disappointing results obtained in nearly all studies that were focused on improving the prognosis of these patients. At this moment the only efficient therapeutic measures for cerebral hemorrhage backed up by scientific proof are the hospitalization in stroke units, the reversal of coagulation abnormalities, and the control of blood pressure.(2)

The experience accumulated by the international scientific community in developing reperfusion therapy for acute ischemic stroke has led to a better understanding of the reasons why significant studies failed to identify treatments efficient for cerebral hemorrhage. At this moment, it is considered that incomplete characterization of the prognostic factors as well as of the predicting factors for secondary cerebral lesions has led to the trial enrolment

of populations of patients for which the investigated therapies couldn't a priori be efficient. Thus, studies for which the main purpose was to limit intracerebral hemorrhage extension have included patients with small hematoma volumes, which we now know have a small risk of secondary growth. On the other hand, studies that evaluated the efficacy of minimally invasive neurosurgical techniques have included predominantly patients with very big hematoma volumes, which have a significant mortality risk even in the first hours of clinical evolution. Persisting in the same error studies that analysed the benefit of haemostatic therapies have included patient populations that presented outside the time window in which these therapies could be efficient. Consequently, a better understanding of the significance of these prognostic factors and the impact of predictors of secondary cerebral lesions in populations of patients with heterogenous aetiologies and characteristics of intracerebral haehemorrhagell contribute to the identification of hyperacute phase therapies which might improve the prognosis of these patients.(2)

The purpose of this paper is to analyse the accuracy of clinical and imaging prognostic factors in a patient population with intracerebral haemorrhage from Romania as well as to identify potential biomarkers which can facilitate the characterization of patients with intracerebral haemorrhage regarding their functional prognosis. The obtained results can significantly contribute to patient selection for different types of acute-phase therapies for which the concrete benefit is influenced by a wide heterogeneity of predictors.

2. Study Objectives

The purpose of this study is the identification of clinical, biological, and imagistic predictors of prognosis in patients with spontaneous cerebral haemorrhage.

To accomplish the objectives of this study the prognosis of the patients was dichotomized into two categories: favorable and non-favourable based on the modified Rankin score at discharge. The other main outcome of the study was in-hospital mortality or survival.

A secondary objective of the study was the characterisation of the volumetric evolution of cerebral perihematic oedema and the identification of the prognostic role of perihematomal oedema in different patient subgroups with spontaneous cerebral haemorrhage.

3. Materials and Methods

This is an observation, cross-sectional cohort study which included patients with intracerebral haemorrhage hospitalized in the Neurology Department of the University Emergency Hospital Bucharest between 01.07.2018 – 01.07.2020.

All the patients hospitalized with an acute intracerebral haemorrhage in the study period were evaluated for inclusion in the study. The diagnosis of intracerebral haemorrhage was based on clinical symptoms and signs of stroke and the computed tomographic decelation of an intraparenchymal hematoma.

Inclusion Criteria: a) Age > 18 years; b) Haemorrhagic stroke diagnosed by clinical land imaging criteria*; c)* Absence of significant subarachnoid haemorrhage, of a subdural or epidural haematoma on the initial CT scan which could suggest the existence of a primary subarachnoid haemorrhage or a traumatic etiology of a brain haemorrhage.

Exclusion Criteria: a) The lack of informed consent (patient or caregiver refusal to utilize the clinical data for a scientific purpose, the patient was not in the conscious state to accept or refuse inclusion in the study and caregivers were not present, lack of informed consent in the medical files of the patient at the time of data collection); b) Low probability of survival of more than 24 hours (appreciated based on initial imaging characteristics of the hematoma and the clinical severity of the patient upon hospital admission); c) Hospitalization in the Intensive Care Department; d) Performance of any neurosurgical procedures immediately after the admission of the patient or during the hospitalization (ventricular drainage, decompressive craniectomy, or any other neurosurgical procedure); e) Initial hospitalisation in another hospital for more than 24 hours and subsequent transfer to the Neurology Department of the University Emergency Hospital Bucharest;

Clinical and ancillary data of the patients were drafted from the medical records, the informatic database of the hospital, and the discharge letter. In some cases, patients and caregivers were contacted at the time of data collection to clarify the lack of disagreement between data. Imaging data were drafted in integrity from the hospital PACS system (Picture Archiving and Communication System).

DICOM images of the computed tomography scans of the patients which were included in the study were imported in Horos v3.36 (Horosproject.org) and Analyze 14 (AnalyzeDirect, Overland Parc; KS., US) and evaluated individually by a sole examiner.

The interpretation of imaging data was performed without the knowledge of clinical and ancillary data of patients and the knowledge of the initial interpretation by the attending radiologist. Each cerebral tomography was reformatted and examined according to the study protocol and a pre-defined algorithm. To re-evaluate the reproducibility and accuracy of measurements twenty aleatory cases were re-analysed by the same examiner and by someone else to establish intra- and inter-observer agreement.

Pentru analiza statistică și reprezentarea grafică a rezultatelor au fost folosite softurile NCSS 2020 Statistical Software (NCSS, LL. Kaysville, Utah, USA) și Medcalc 18.11.3 Statistical Software (MedCalc Software, Ostend, Belgium).

The distribution of continuous variables was appreciated with the help of the D'Agostino-Pearson test and based on individual histograms. Continuous variables with non-normal distribution were presented as median and 25-75 interquartile range (IQR). Continuous variables with normal distribution were presented as mean and standard deviation. For comparisons between variables with normal distribution the ANOVA and Student t-test were used based on the number of groups analysed. For comparisons between non-normal variables, Mann-Whitney and Kruskal-Wallis tests were used based on the number of groups analysed.

To test the association between categorical variables we used the Chi-squared and Fischer exact tests, based on the number of observations analysed.

For the multivariable analyses, we performed logistic regression models in which we included as independent variables clinical, biological and imagistic factors previously shown to be predictors of prognosis in intracerebral haemorrhage and which in the univariate analysis of our cohort were identified to have a p-value of ≤ 0.1 together with the factor for which we sought to obtain the independent predictive value. We used as a dependent variable for these logistic regression models the in-hospital mortality variable as well as the dichotomized mRS at discharge 0-2:good prognosis, 3-6 bad prognosis. As a means to introduce the dependent variables, we used the Enter variable. The performance and concordance of the logistic regression models were analysed using the Hosmer – Lemeshow test as well as the *Cox and Snell* R^2 and *Nagelkerke* R^2 parameters.

We analysed with the help of ROC curves (Receiver operating characteristics) the performance of different clinical, biological, and imaging variables in predicting patient prognosis. With the help of the Youden index and an associated numeric criterion, we have

decided the best value of the analysed predictor that was associated with a good sensibility and specificity in each analysis.

To prove that the statistical association was not due to chance the null hypothesis was refuted. The corresponding statistical significance value was considered as a value of $p<0.05$.

4. Results

The initial patient population included in the study consisted of 270 patients hospitalized with a diagnosis of acute hemorrhagic stroke in the Department of Neurology of the University Emergency Hospital Bucharest during the study period, which was eligible based on the study inclusion criteria. For all of these patients, the aetiology of the intracerebral haemorrhage was established in conformity with the SMASH-U criteria.(3) 218 patients representing 80.7% of the study population were classified in the spontaneous cerebral haemorrhage group (149 patients – 55.2% intracerebral haemorrhage secondary to hypertension-related small vessel disease, 16 patients – 5.9% secondary to amyloid angiopathy, 6 patients – 2.2% secondary to other systemic diseases, 47 patients – 17.4% secondary to undetermined aetiology). 52 patients representing 19.3% of the study population were classified in the secondary intracerebral haemorrhage group. The final analysed patient group was represented by the 218 patients included in the spontaneous intracerebral haemorrhage group.

The median patient age of the patients included in this group was 69 years (25-75 IQR, 59-78). 98 (44.9%0 of these patients were female. The previous neurologic disability of the patients was good, with median Rankin scores of 0 points (25-75 IQR, 0-0). The neurologic severity at hospital admission was moderately severe with a median NIHSS score of 15 (25-75 IQR, 5-22) and a median GCS of 15 (25-75 IQR, 9-15). 165 (75.6%) of the patients had a history of arterial hypertension, 67 (30.7%) had a history of diabetes mellitus, 140 (64.2%) had a history of dyslipidemia, 38 (17.4%) had a history of stroke, 16 (7.1%) had a history of atrial fibrillation and 11 (5.1%) and 11 (5.1%) had a history of coronary heart disease. Only 99 (45.5%) were following an antihypertensive treatment before the index stroke and 55 (22.2%) were following an antiplatelet treatment before hospitalization.

Concerning the imaging characteristics of the study population, the median hematoma volume at admission was 10.59 ml (25-75 IQR, 3.46-31.03 ml). Imaging data at 3 days ± 12 hours were available for 131 patients (out of 188 who survived until this moment,

representing 70% of the initial cohort). Imaging data at 6 days ± 24 hours was available for 115 patients (out of 172 patients who survived until this moment, representing 66.8% of the initial cohort). Finally, imaging data at 10 days ± 24 hours was available for 104 patients (out of 157 patients who survived until this moment, representing 66.2% of the initial cohort).

During hospitalisation, out of the initial cohort, 80 patients (36.7%) died. The median time elapsed between hospital admission and death was 5.1 days (25-75 IQR, 1.89-9.82). Out of these patients, 30 (37.5%) died during the first 3 days, 16 patients (20%) died during the subsequent 3-6 days, 15 patients (18.75%) died during the subsequent 6-10 days and 19 patients (23.75%) died after 10 days of hospitalisation. The median hematoma volume at admission for patients who died was 29.49 ml (25-75 IQR, 11.1-60.7). The mRS score at discharge had a non-normal distribution, the median mRS score was 4 points, with 50% of the patients having scores between 2 and 6. The patients with mRS scores 0,1,2 were included in the favourable prognosis group (n=62, 28.43%) while the patients with mRS scores of 3,4,5,6 were included in the un-favourable prognosis group (n=156, 71.57%).

The age of the patients who died during hospitalisation was significantly bigger compared to the age of the patients discharged from the hospital (median patient age 71 years vs. 67.5 years, p=0.009). Furthermore, to appreciate the magnitude of the association between the patient age and the risk of in-hospital death for patients with intracerebral haemorrhage included in our study, we have used a logistic regression model in which we have introduced as independent variables the parameters of the ICH score (age, initial hematoma volume, GCS at admission, ventricular effraction, supra or infratentorial localisation of ICH) while we considered as dependent variable in-hospital mortality. The model of regression had the following parameters: $\chi 2(5)=114.26$, $p<0.0001$, test Hosmer & Lemeshow:$\chi 2=7.69$, $p=0.46$. (see Table 1)

Table 1. Multivariable analysis for the relationship between age and in-hospital mortality

Variable	Coeficient	Standard error	P value	OR	95% CI
Age	0.06	0.01	**0.0005**	1.069	1.029 – 1.109
Initial hematoma volume	0.04	0.01	< **0.0001**	1.048	1.025 – 1.072
Localisation of ICH*	0.26	0.66	0.6	1.29	0.35 – 4.8
Ventricular effraction	0.46	0.42	0.2	1.59	0.69 – 3.67
Admission GCS	- 0.35	0.07	< **0.0001**	0.698	0.606 – 0.805
Constant	- 1.9	-	-	-	-

** supratentorial versus infratentorial*

Using the Mann-Whitney test we evaluated a possible association between absolute glycaemic values at admission and patient prognosis. Admission glycaemia was significantly higher in patients who died during hospitalisation as opposed to discharged patients (median values 163 mg/dl vs. 126 mg/dl, p<0.0001). The values of this parameter were significantly higher for patients discharged with an mRS score of 3-6 as opposed to patients discharged with an mRS score of 0-2 (139.5mg/dl vs. 121 mg/dl, p=0.01).

Because national and international guidelines for the treatment of acute stroke recommend glycaemic values to be maintained at values lower than 180mg/dl we have analysed if there is an association between glycaemic values > 180mg/dl at admission and the prognosis of patients with spontaneous intracerebral haemorrhage. We have found no significant association between values > 180mg/dl and mRS score at discharge (mRS 0-2 vs. mRS 3-6, 23.2% vs. 19.3%, p=0.5). However, patients which died during hospitalisation had significantly more frequent glycaemic values > 180mg/dl compared to who patients were discharged (13.4% vs. 8.8%, p=0.0001).

To appreciate the magnitude of the association between glycemia value at admission and the risk of in-hospital death for patients with spontaneous cerebral haemorrhage included in our study, we have built a logistic regression model in which we have introduced as independent variables the parameteres of the ICH score (age, initial hematoma volume, admission GCS, ventricular effraction and localisation supra – or infratentorial) and glycemia. The dependent variable in this model was death during hospitalisation. The model had the following parameters: $\chi 2(6)=122.4$, p<0.0001, test Hosmer & Lemeshow: $\chi 2=7.02$, p=0.53.

Table 2. Multivariable analysis for the relationship between admission glycemia and in-hospital death

Variable	Coeficient	Standard error	P value	OR	95% CI
Age	0.07	0.02	**0.0001**	1.08	1.03 – 1.126
Initial hematoma volume	0.04	0.01	**< 0.0001**	1.05	1.026 –1.075
Localisation of ICH*	0.34	0.7	0.6	1.41	0.35 – 5.6
Ventricular effraction	0.24	0.44	0.5	1.27	0.52 – 3.05
Admission GCS	- 0.35	0.07	**< 0.0001**	0.698	0.604 – 0.805
Glycemia	0.008	0.003	**0.01**	1.008	1.001 – 1.014
Constant	- 3.9	-	-	-	-

** supratentorial versus infratentorial*

The results of this multivariable analysis prove that glycemia is together with age, admission GCS, and the admission hematoma volume an independent predictor of death during hospitalisation in our cohort

If all the parameters included in the regression model were constant, for each mg/dl increase in blood glucose the risk of in-hospital mortality increases by 0.8%, and for each 10 mg/dl increase in blood glucose the risk of in-hospital mortality increases with 8.3%.

To estimate a value of glycemia that permits a balanced orientation for the risk of in-hospital mortality we have performed a ROC analysis. Thus, we have obtained a Youden index J of 0.352, the criterion chosen was glycemia higher than 144mg/dl. The parameters of this test were: AUC 0.697, standard error 0.03, 95% CI 0.63-0.75, z= 5.28, p=<0.0001.

The neutrophil/lymphocyte ratio (NLR) evaluated at admission was significantly higher in patients that died during hospitalisation as compared to the group of patients who survived (median 5.3 vs. 3.8, p=0.002). We have also identified a significant association between admission NLR and the functional prognosis of the patients included in our cohort (median 4.4 for patients with unfavourable prognosis vs. 3.6 for patients with favourable prognosis, p=0.03).

To identify the independent prognostic value of NLR as a predictor of mortality during hospitalisation, for patients included in our cohort we have to build a multivariable analysis model in which age, initial hematoma volume, GCS at admission, and NLR were included as variables. The parameters of this model were: $\chi 2(4)=105.094$, $p<0.0001$, test Hosmer & Lemeshow:$\chi 2=8.09$, p=0.42. Our results did not show that NLR at admission is an independent predictor of in-hospital death (OR 1.09, p=0.06, 95% CI 0.99-1.21).

For the 117 out of 188 patients who survived during the first 72 hours and for which data about leucocytes and neutrophils were available at 72 hours, we have analysed the relationship between NLR at 3 days after admission and prognosis. We have identified a median NLR value at 3 days, for the 34 patients which survived in the first 3 days but afterward died significantly higher than the median NLR value of 83 patients who have survived (10.7 vs. 5.3, $p<0.0001$). Furthermore, the 89 patients discharged with mRS scores 3-6 had a significantly higher median NLR at 3 days compared to patients discharged with mRS 0-2 (6.3 vs. 3.4, $p<0.0001$).

To appreciate if the NLR at 3 days is an independent predictor of death during hospitalisation, we have used another regression model in which we have introduced independent variables: age, initial hematoma volume, GCS at admission, and NLR at 3 days and as dependent variable: in-hospital death. The parametres of this model were: $\chi 2(4)=51.4$,

p<0.0001, test Hosmer & Lemeshow:$\chi 2$=6.1, p=0.6. We found that NLR at 3 days is an independent predictor of in-hospital death (p=0.0003, OR 1.26, 95% CI 1.1-1.4).

For patients included in the study population, admission Glasgow score was significantly associated with in-hospital mortality (p<0.0001) and un-favourable functional outcome (p<0.0001). The results of the multivariable analysis presented in Table 1, have shown that admission GCS is also an independent predictor of in-hospital mortality, for each 1-point increase in admission GCS the risk of death during hospitalisation decreases by 31% (OR 0.69; CI 0.6-0.8). To estimate the best value of the GCS that orients towards the risk of in-hospital death, we have performed a ROC analysis. Thus, we have obtained a Youden J index of 0.548, with an associated criterion of GCS ≤ 13 points. The parameteres of this test were: AUC 0.818, standard error 0.03, 95% CI 0.75-0.86, z= 10.3, p < 0.0001.

With regards to the clinical severity at admission evaluated using the NIHSS score, we have identified a significant association with the functional outcome at discharge as well as in-hospital mortality. Thus, in the group of patients with the un-favourable outcome at discharge, the admission NIHSS was significantly higher as opposed to the group of patients with favourable outcome (median 19 points vs. 4 points, p<0.0001). The median NIHSS score at admission in the group of patients who died during hospitalisation was significantly higher as opposed to the group that was discharged. To appreciate the independent predictive value for the risk of in-hospital death, for the NIHSS score, we have constructed a multivariable logistic regression model in which we have included as independent variables the components of the ICH score and we have switched the GCS with the NIHSS score. The model had the following parameters: $\chi 2(5)$=114.43, p<0.0001, test Hosmer & Lemeshow: $\chi 2$=4.39, p=0.8. Thus, we have obtained an OR of 1.14 (95% CI 1.08-1.2, p<0.0001). Consequently, if all other variables are constant for eac1-pointnt increase in the NIHSS score the risk of death during hospitalisation increases by 14% a,nd for each 10-point increase in the NIHSS score the risk of death increases by 3.7 times.

To estimate a value for which the NIHSS can be used to better predict the risk of in-hospital death, we have performed a ROC analysis. Thus, we have obtained a Youden J index of 0.544, for an associated NIHSS score > 19 points. The parameters of this test were: AUC 0.844, standard error 0.02, 95% CI 0.78-0.89, z=11.97, p<0.0001.

The ICH score represents a synthesis of the primary identified prognostic factors in ICH. In the current study, it was significantly associated with prognosis at discharge. The

median ICH score in the subgroup of patients who died during hospitalisation was 2 as compared to 1 in the subgroup of patients who survived ($p<0.0001$). About the relationship between the ICH score and the functional prognosis at discharge, this score had significantly higher values in the group of patients presenting with an un-favourable prognosis as compared to the group of patients who presented a favourable prognosis (median value 1 vs. 0, $p<0.0001$).

The results of the implementation and validation of the ICH score offer a good estimate of the risk of death during the first 30 days of clinical evolution for each variable of this score. We have comparatively analysed the values provided by this study with the values obtained for our cohort and represented them in Table 3.

Table 3. Comparison between in-hospital mortality in the study population and the 30-days mortality estimated in the initial ICH paper (4)

	30-days mortality ICH estimate	**In-hospital mortality Current cohort**
Score ICH = 0	0%	5.8% (69 patients)
Score ICH = 1	13%	27.3% (66 patients)
Score ICH = 2	26%	59.5% (37 patients)
Score ICH = 3	72%	90% (20 patients)
Score ICH = 4	94%	100% (10 patients)
Score ICH = 5	100%	100% (2 patients)

The patients that died during hospitalisation had significantly higher hematoma volumes at admission as compared to survivors (median value 29.5 ml vs. 5.3ml, $p<0.0001$). This important association between the vital prognosis and hematoma volume was also identified with regard to functional outcome. Patients with un-favourable functional outcomes had significantly higher hematoma volumes as compared to the patients with favourable prognosis (16.8 ml vs. 1.8 ml, $p<0.0001$). The results of the multivariable model which has included all the ICH parameters and is represented in Table 1, have shown that the admission hematoma volume is an important predictor of in-hospital death for the study population. For each ml increase in admission hematoma volume, the risk of in-hospital death grows by 4.8% and the increase in hematoma volume by 10 ml is associated with a 59% increase in risk of in-hospital death.

The irregular shape of the hematoma (Barras categories III, IV, and V) was identified on admission native brain CT images for 97 patients (45.9%) of our study cohort. We have analysed the relationship between the shape of the cerebral hematoma and the patient prognosis and have found that the in-hospital rate of death is higher in patients with irregularly shaped hematomas as compared to patients with regular-shaped hematomas

(59.8% vs. 16.7%, p<0.0001). Similarly, patients with irregularly shaped hematomas very significantly more frequently discharged with mRS scores of 3 – 6 as compared with patients with regular-shaped hematomas (92.8% vs. 54.4%, p<0.0001).

We used multivariable analyses to assess the independent predictive value for in-hospital mortality and the prognosis at discharge, regarding the shape of hematoma on admission brain CT scan. The logistic regression model included the following variables: age, GCS score at admission, initial hematoma volume, and the shape of the hematoma (regular vs. irregular). The dependent variable was in-hospital death. The model had the following parameters: $\chi 2(4)=116.75$, p<0.0001, test Hosmer & Lemeshow: $\chi 2=10.5$, p=0.2. We found that in our cohort, the initial hematoma shape is an independent predictor of in-hospital death, the irregular shape raises the odds of death during hospitalisation by 2.6 times (OR 2.6, p=0.04, 95% CI 1.02-7.2).

Similarly, the density of the hematoma was visually appreciated for all the patients in the study population on admission native CT images and was classified according to the Barras Scale.(5) For 77 patients representing 36.5% of the study cohort, we found inhomogeneous hematomas (Barras categories III, IV, V). The mortality during hospitalisation was significantly higher for patients with inhomogeneous hematomas as compared to homogeneous (63.6% vs. 20.9%, p<0.0001). Furthermore, 92.2% of the patients with inhomogeneous hematomas had mRS scores between 3-6 at discharge as compared to 60.4% of those with homogenous hematomas (p<0.0001).

We analysed the independent predictive value of in-hospital death for the homogeneity of the hematoma with the help of a logistic regression model in which independent variables were: age, GCS at admission, initial hematoma volume, and homogeneity of the hematoma (inhomogeneous vs homogenous). The dependent variable was in-hospital death. The model had the following parameters: $\chi 2(4)=116.75$, p<0.0001, test Hosmer & Lemeshow: $\chi 2=5.9$, p=0.6. We found that in our study cohort, the homogeneity of the hematoma is an independent predictor in-hospitalal death, these aspects raised the chances of in-hospital death by 2.7 times (OR 2.7, p=0.04, 95% CI 1.008-7.2).

Furthermore, we have analysed the independent prognostic value of the extension of the hematoma volume at 72 hours, by introducing the data available for the 131 patients in a multivariate model in which independent variables were : age, initial hematoma volume, and the presence or absence of extensions. The dependent variable for this model was the

risk of in-hospital death during hospitalisation. The model had the following parameters: $\chi 2(3)=147.879$, $p<0.0001$, test Hosmer & Lemeshow: $\chi 2=3.4$, $p=0.9$. We have concluded that when adjusting for age and initial hematoma volume, the presence of hematoma extension at 72 hours raises the risk on hospital death 4 times.

We have also analysed the relationship between the absolute perihepatic edema volume and the in-hospital mortality and we have observed that the median absolute perihematic edema was significantly higher in patients who died during hospitalisation as opposed to patients who survived. This was true for patients at admission, at 3 days ± 12 hours and at 6 days ± 24 hours. The results are presented in Table 4.

Table 4. The relationship between absolute perihematic oedema and in-hospital death at different time points (univariate analyses)

	General	Patients who survived (n=125)	In-hospital death (n=72)	P-value
PE volume at admission [1]	6.6 (1.6 – 17.7)	4.2 (0.9 – 10.4)	15.6 (5.1 – 35.5)	< 0.0001
PE volume at 3 days ± 12 hours [2]	15.2 (5.1 – 40.7)	11.4 (2.9 – 28.5)	37.7 (13.1 – 69.4)	0.0002
PE volume at 6 days ± 24 hours [3]	18.1 (6.1 – 53.1)	15.4(3.5 – 43.2)	47.6 (16.1 – 96.4)	0.002
PE volume at 10 days ± 24 hours [4]	21.6 (9.7 – 58.3)	20.9 (8.5 – 54.3)	31.2 (15.3 – 100.1)	0.2

Data are expressed as median and 25-75 IQR
[1] – Calculated for 197 patients; [2] – Calculated for 123 patients
[3] – Calculated for 107 patients; [4] – Calculated for 98 de patients

Concerning the relationship between the volume of perihematic oedema and the prognosis of the analysed patients, we have observed significantly higher perihematic oedema volumes in patients discharged with mRS scores of 3-6 as compared with patients discharged with mRS scores of 0-2 for all the timespans analyzed. The data are presented in Table 5.

Table 5. Relationship between perihematic oedema volume and functional prognosis at discharge at different time points (univariate analysis)

	General	Patients discharged mRS 0-2 (n=51)	Patients discharged mRS 3-6 (n=146)	P-value
PE volume at admission [1]	6.6 (1.6 – 17.7)	0.9 (0.5 – 4.1)	10.1 (3.7 – 23.6)	< 0.0001
PE volume at 3 days ± 12 hours [2]	15.2 (5.1 – 40.7)	2.5 (1.3 – 10.4)	24.9 (10.1 – 48.9)	< 0.0001
PE volume at 6 days ± 24 hours [3]	18.1 (6.1 – 53.1)	2.9 (0.9 – 13.4)	36.5 (14.3 – 63.2)	< 0.0001
PE volume at 10 days ± 24 hours [4]	21.6 (9.7 – 58.3)	8.7 (0.8 – 16.1)	35.5 (13.4 – 77.7)	< 0.0001

Data are expressed as median and 25-75 IQR
[1] – Calculated for 197 patients; [2] – Calculated for 123 patients
[3] – Calculated for 107 patients; [4] – Calculated for 98 de patients

Furthermore, we analysed the independent predictive value for in-hospital death and functional outcome at discharge for the absolute perihematic oedema volume at the different

pre-defined time points. We have constructed separate models of logistic regression which have included as independent variables: initial hematoma volume and the volume of perihematic oedema at the pre-specified time point and as dependent values the survival status at discharge and the functional prognosis at discharge. Data are presented in Table 6.

Table 6. Relationship between perihematic oedema volume and in-hospital death a pre-specified time points (multivariable analyses)

	P-value
PE volume at admission [1]	0.8
PE volume at 3 days ± 12 hours [2]	0.3
PE volume at 6 days ± 24 hours [3]	0.6

[1] – Calculated for 197 patients; [2] – Calculated for 123 patients
[3] – Calculated for 107 patients;

Furthermore, we have analysed the absolute perihematic oedema volume 3 days after admission for patients who have died during hospitalisation and for survivors with regard to the initial hematoma volume. We have shown that in patients with initial hematoma volumes bigger than 30 ml, the 3 days ± 12 hours perihematomal oedema volume was bigger in patients that died during hospitalisation as compared to patients that survived but this difference did not attain statistical significance (median volumes of 67.9 ml vs. 55.9ml, p=0.2, Figure 1).

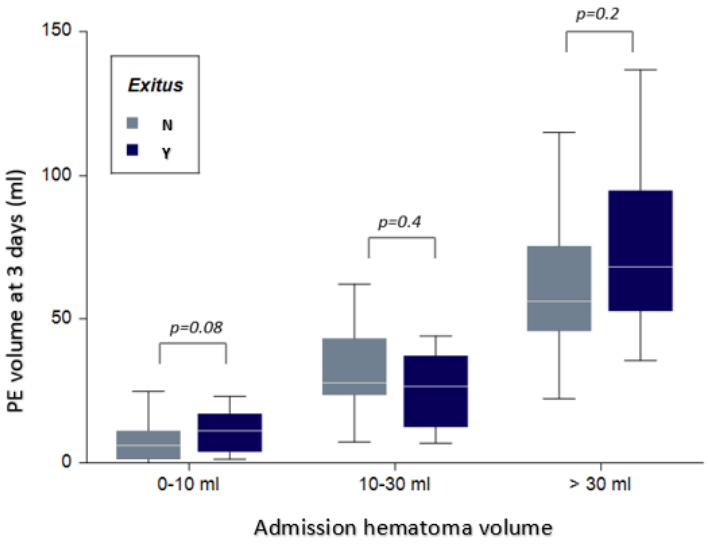

Figure 1. Perihematic Edema Volume at 3 days ± 12 hours with regard to the initial admission hematoma volume and in-hospital death

The rate of perihematic oedema expansion at 3 days ± 12 hours, at 6 days ± 24 hours, and at 10 days ± 24 hours was calculated based using as reference the initial computed tomography.

The median rate of expansion of the perihematic oedema at 3 days ± 12 hours was 0.30ml/h in the group of patients who died during hospitalisation and 0.09ml/h in the group of patients who have survived (p=0.0004). A significantly higher perihematomal expansion rate in patients who died during hospitalisation as opposed to survivors was obtained also at 6 days ± 24 hours (0.2ml/h vs. 0.07 ml/h, p=0.0006). Concerning the perihematomal expansion rate at 10 days ± 24 hours, the results have shown similar results between patients that subsequently died during hospitalisation and survivors (0.08 ml/h vs. 0.06ml/h, p=0.2).

5. Discussion

The aim of this study was to analyze the accuracy of clinical, biological and imaging prognostic factors in a population of patients with ICH from Romania and to identify the potential of this biomarkers in facilitating the characterization of patients with ICH from a functional prognosis point of view. The results can significantly contribute to the selection process of patients for different kinds of acute phase therapies, for which the benefit is influenced by as of yet undefined factors.

The in-hospital mortality in our cohort was 36.7%. 37.5% out of our patients died during the first 72 hours, 20% during the first 3-6 days, 42.5% after six days from the moment of admission. The mortality during the early hospitalization is tightly linked to the volume of ICH and the studies done over the past 30 years have shown that the mortality in the first 24-72 hours has remained largely unchanged despite improvements in acute care(6). The mortality percentages in our study were higher compared to the literature, which shows that one in three patients with ICH dies during the first 30 days from disease onset, this fact is probably related to the lack of craniectomies in our hospital as well as to a lack of developed nursing measures which are present in developed systems (6).

The functional prognosis at discharge was appreciated using the modified Rankin score, scores 0-2 were included in the good prognosis group. 28.4% of the study population was discharged with mild neurologic deficits, which are similar to percentages reported in the literature – between 12% and 39% of patients presenting functional independenc at 30 days from the index event (1,7,8).

At this moment, the most wide-spread instrument for predicting mortality at 30 days in patients with ICH is the ICH score, which includes the admission GCS, the initial hematoma volume, age, localization (supra or infratentorial) and ventricular effraction(4). Results of the implementation and validation studies of this score estimate a risc of death

during the first 30 days of 97% for scor 5 and 72% for score 4. These rates of mortality are associated with high ICH scores and have remained unchanged during the past years, which is a confirmation of the excellent predictive value of this score but also reflects the lack of new acute phase therapies that can improve prognosis (9). In our cohort the rate of mortality of patients with ICH scores of 4 and 5 was 100% but given the small sample size (n=12), we cannot draw serious conclusions about associated mortality in patients with large scores. However, we have shown that there is an increase mortality in our hospital as compared to the estimated mortality in patients with low ICH scores. Thus, for ICH 0 – our rate was 5.8% compared to 0%, for ICH 1 our rate was 27.3% compared to 13%, for ICH 2 our rate was 59.5% compared to 26% and for ICH 3 our rate was 90% compared to 72% (4). These mortality rates in patients with small ICH scores, compared co mortality rates estimated in developed nations with more developed heatlh-care systems probably represent the lack of resources in the hospital in which this study was performed. They should prompt further analysis as to the real cause of death in these patients.

The median age of the patients in our study was significantly greater in the group of patients that died during hospitalization as compared to the survivors (71 years vs. 67.5 years). In an analysis of the INTERCAT-2 study, which included 2794 patients with ICH, the initial clinical severity has grown with age and lobar location. Ventricular effraction was also more frequent in the elderly. This analysis demonstrated that patients with ICH over 75 years of age have a significantly higher risk of mortality and disability as compared to those with median ages of 52 years (OR 4.3, 96% CI 3.1-6.1) (10). In our analysis age was an independent predictor of in-hospital death.

The GCS is a largely used score, both in the pre-hospital and hospital environment for the estimation of prognosis of patients with cerebral lesions of different etiologies. In our study, the GCS at the time of admission was an independent prognosis of in-hospital death.

The NIHSS score was first implemented in order to appraise the severity of acute ischemic stroke, and was proven effective in many publications over the last 25 years as a predictor of mortality and prognosis for stroke patients(11,12). Using this score for patients with hemorrhagic stroke is far more restricted, studies that aimed to validate the utility of NIHSS for ICH being limited. Recent data have shown a higher performance for predicting prognosis of ICH for NIHSS as compared to GCS(13). The hesitancy to use the NIHSS might be explained by the high familiarity of intensive care, emergency, neurosurgery

doctors with the GCS and the lower familiarity with the NIHSS but also by the influence of the loss of consciousness which is more frequently encountered in patients with ICH due to ventricular effraction. The NIHSS score can be more useful according to our data for patients with small hematomas, without mass effect and ventricular effraction. Literature data suggests that patients with ICH and NIHSS scores higher than 18 points have a 30 days mortality rate that reaches 82%(14).

We analyzed the predictive value of NIHSS for in-hospital death with regard to the initial hematoma volume and have shown that NIHSS is a valuable predictor irrespective of hematoma volume but that the best predictive value is in patients with hematomas < 10 ml. The results of this statistical analysis have shown a specificity of 100% for NIHSS scores > 25 in patients with hematomas of > 30ml but this result has to be interpreted with caution due to the relative low number of patients in this subgroup. In our study NIHSS was also significantly associated with prognosis at discharge, with an baseline value of > 6 points that is associated with a sensibility of 90% and a specificity of 75% in predicting an unfavourable outcome.

In our study the prediction of in-hospital death was similar between the NIHSS and GCS score (AUC 0.846 versus AUC 0.818, p=0.3), but similar to other data from the literature the predictive value for unfavorable functional prognosis was better for the NIHSS score (AUC 0.846 versus AUC 0.818, p=0.3) (13).

Many studies performed up to this point aimed to identify biological parameters for the outcome of ICH patients. The most widely identified predictor was glycemia. In our study, blood glucose values were significantly higher in patients that died during hospitalization as opposed to the patients that survived (median values 163 mg/dl vs. 126 mg/dl, p<0.0001). The values of this biological parameter were significantly higher in patients discharged with mRS 3-6 as compared with patients with mRS 0-2 (139.5 mg/dl vs. 12 mg/dl, p=0.01). Admission blood glucose remained an independent predictor of in-hospital death even adjusting for parameters of the ICH score. In a subgroup analysis of the INTERACT-2 trial, patients with high glycemic values during the first hours were more frequently female, had more frequently diabetes mellitus, higher blood pressures, cortical hematomas, higher admission hematoma volumes, greater clinical severity and developed more frequently ventricular efraction. The conclusion of this study was that the high values of glicemia in patients with ICH are the consequences of the early neurologic deterioration

and are sustained by the fact that these patients more frequently develop hemorrhagic extension and greater overall brain edema(13).

For our cohort, neutrophil, limfocite and NLR at the time of admission were higher in patients with in-hospital death as compared to survivors but this parameters were not independent predictors of death during hospitalization after adjusting for age, hematoma volume, GCS at admission.

The NLR ratio calculated based on the 72 hours blood sample had higher values in patients that survived in the first 72 hours but died later as compared to the patients that were discharged alive (10.7 vs. 5.3, $p<0.0001$). This ratio maintained his value as an independent predictor of in-hospital death, even after adjusting for age, hematoma volume and admission GCS score. This discrepancy between the prognostic value of NLR at three day and the prognostic value at admission may be explained by the small time span between ICH onset and arrival at the emergency unit. This time would be insufficient to permit a neuro-imune activation and to thus reduces the utility of admission NLR as a predictor of mortality. (15) Given this clinical results, the low cost and the ubiquity of blood analysis, the dynamic NLR represents a useful fashion to appreciate the prognosis of patients with ICH and to identify patients at risk of death during hospitalization(16,17).

In our study, the median hematoma volume at admission was 10.6 ml, 50% of the patients had hematomas between 3.5 ml and 31 ml. This median hematoma volume is similar to other big randomized studies that have analyzed the effects of different pharmacological measures on outcome, 13 ml in TICH-2, 11 ml in INTERACT 2 and 10 ml in ATACH2(18–20). The hematoma volume for patients in our study was significantly greater in patients that died as compared to survivors (29.5ml vs 5.3ml, $p<0.0001$) and this difference has remained significantly even after adjusting for other parameters of the ICH score. The initial hematoma volume was an independent predictor of unfavorable prognosis, after adjusting for this components : OR 1.13, 95% CI 1.07-1.2, $p<0.0001$). The majority of data from the literature has used a baseline value of 30 ml of hematoma to predict a unfavourable prognosis. In our study mortality during hospitalization was 71.7% in patients with hematoma volumes greater than 30 ml but the baseline value that best oriented towards an unfavourable outcome was 7 ml sensibility 85.7% and specificity 58.6%, AUC 0.799, $p<0.001$). For a given patient population with our characteristics, the baseline value of 30ml predicts in hospital death with a sensibility of 49.4% and a specificity of 89.5%

corresponding to a positive predictive value of 71%. Thus, using this baseline value as a sole inclusion criterion for patients who might benefit from acute interventional therapies may lead to biased selection leading to false negative results.

In our study the absolute perihematic edema volume was significantly higher in patients that died during hospitalization as compared to survivors at all time points. However, when these results were adjusted for the initial hematoma volume, the absolute perihematic edema did not prove to be an independent predictor of in-hospital death regardless the time-point. The perihematic edema volume was also significantly greater in patients discharged with mRS 3-6 compared to mRS 0-2 but in all the moments analyzed after adjustement it remained significantly associated with outcome just at hospitalization with an OR of 0.01, 95% CI 0.85-0.98, p=0.01. Thus, each increase in 1 ml leads to lower chances of good functional outcome by 9%.

Perihematic edema represents an attractive target for many therapies aiming to improve the outcome of patients with ICH. (21) The literature data shows that the edema starts to develop during the first hours and reaches a maximum at 3-6 days after onset, after that it has a variable evolution depending on the severity of secondary associated injuries(22). However, the relationship between edema and prognosis is not well studied and the few studied that reported a significant association between perihematic edema volume, the rate of perihematic edema volume and the prognosis of patients with ICH have utilized complicated statistical models which included many artificial calculations and which have not incluced clinical predictors in the models (23).

Because several studies performed until this moment have suggested that sometimes perihematic edema can have a disproportionate volume as compared to the volume of the ICH, we have examined the role played by relative perihematic edema in our study. Which is defined by the ratio between the absolute perihematic edema and the volume of the ICH. The median value of relative perihematic edema at admission was 0.6, at 3 days 1.7, at 6 days 2.5 and at 10 days 4.9. We have analysed the relationship between this ration and death during hospitalization and have found that the median relative perihematic edema at admission is similar in patients which died compared to those who survived (0.5 vs. 0.6, p=-2). The median perihematomal edema value at 3 and 6 days after admission was significantly higher for patients who died during hospitalization, but when we tried to adjust for admission hematoma volume, relative edema did not remain an independent predictor of outcome or

death at neither examined time point. These results are partly similar to those obtained by Gebel et al. who showed that relative edema at admission is not an independent predictor of death but of functional outcome. (21) This difference may be attributed to errors in measuring as well as to different patient populations.

Another parameter that was appreciated was the impact of the rated of cerebral edema expansion on prognosis of patients at 3, 6 and 10 days. This analysis had the assumption that o higher edema expansion rate is associated with a higher in-hospital death. .(23) The median rate of perihematomal edema expansion at 3 days was 0.3ml/h in patients who died as compared to 0.09 ml/h in patients who survived (p=0.0004). The perihematomal expansion rate was also significantly higher in patients who died as compared to survivors at 6 days (0.2ml/h vs. 0.07 ml/h, p =0.0006) but not at 10 days (0.08 ml/h vs. 0.06ml/h, p=0.2). When we adjusted for initial hematoma volume we found that the edema expansion rate is not an independent predictor in our cohort, the association between this variables is probably due to the fact that higher hematoma volumes lead to higher edemas and subsequently to higher expansion rates. In consequence in order to obtain solid results for this value a study has to include homogenous patients groups in terms of admission hematoma volumes and clinical severity.

6. Study Limits

- The study had several limits related to the type of the study and the methodology.
- The patient population has not included many patients with large hematoma volumes for which the risk of survival more than 24 hours was very low, due to the fact the imaging re-evaluation at the pre-specified time points could not have been pursued. The exclusion of this category of patients from our study resulted in an overall lower median hematoma volume and lower overall mortality rate compared to the observed mortality rate when all patients with intracerebral haemorrhage from our department are analysed.
- The functional prognosis of the patients from our cohort was appreciated using the modified Rankin Score at discharge and not at 3 months. Given that for a small but significant percentage of patients with intracerebral haemorrhage the neurologic state can improve with rehabilitation during this time firsts months, the analysis of an mRS at 3 months probably better reflects the medium and long-term functional status of these patients. The bad performance scores of the multivariable models for this dependent value might be explained by this methodological issue.

- The re-examination using computed tomography at all pre-specified time points for all the patients included in the study that has survived until that moment was not possible. This limitation has led to the shrinkage of our patient population available for studying some clinical, biological, and imaging variables. This also led to the limitation with regard of independent variables that could be included in the multivariable models.
- It was not possible to obtain some biological parameters like the C reactive protein for all patients included in the study, which has made the analysis of the association between these parameters and the clinical and imaging variables of the patients difficult.
- Even if at this moment automatic measuring techniques of the hematoma volume and the perihematomal oedema are used in clinical studies, these techniques could not be used in our patient population due to difficulties by which other authors have been confronted. (24). It was sometimes due to the low quality of the scans, impossible to clearly differentiate between leukoaraiosis and cerebral oedema and sometimes impossible to clearly delineate cerebral oedema from mass effect. Another encountered problem was the delineation of the intraparenchymal haematoma and the ventricular effraction. Thus, we have utilised a semiautomatic technique to measure these hematoma volumes, even if this technique is time consumptive in comparison with the recommended automatic segmentation techniques.(24–26)

7. Conclusion and personal contribution

This study is one of the few studies that evaluated the accuracy of clinical, biological, and imaging factors as outcome predictors in a population of patients with intracerebral haemorrhage from Romania. It is also one of the few studies that have analysed the significance of the clinical impact of perihematic oedema in a population that was followed up for ten days.

The median age of our cohort was 69 years, significantly smaller than that of other populations with intracerebral haemorrhage reported from developed countries.

The in-hospital mortality was 36.7%. 37.5% of our patients have died during the first 72 hours of hospitalisation, 20% have died in the 3 to 6 days interval, 42.5% have died after 6 days from hospital admission. 71.6% of our study population had an un-favourable functional outcome at discharge.

The mortality rate of patients with intracerebral haemorrhage with small ICH scores was approximately two times higher than the mortality rate estimated by the ICH score.

The age of the patients and the initial severity of intracerebral haemorrhage were the principal prognostic factors for in-hospital mortality in our study.

In a population of patients with intracerebral haemorrhage with similar characteristics as in our study, for each 10 years increase in the age of the patients the risk of in-hospital death increased by 11.7 times. The value that orients best towards the risk of in-hospital death in our cohort is 78 years.

The principal clinical factors associated with in-hospital death were age and initial clinical severity of the intracerebral haemorrhage.

The Glasgow and NIHSS scores had similar predictive values for in-hospital death, but the NIHSS score had a superior value for identifying an unfavorable functional outcome.

The main biological predictors of prognosis, out of those analysed in our study were glycemia and neutrophil to lymphocyte ratio at 72 hours.

For a given patient population, with similar characteristics as ours, the increase in serum blood glucose by 10mg/dl leads to an increase in the risk of in-hospital death by 8.3%. The value of blood glucose that best orients upon the risk of in-hospital death during the first days of clinical evolution is 144mg/dl.

A value of > 6.3 of the neutrophil to lymphocyte ratio at 3 days has been predicted with a sensibility of 82.4% and a specificity of 75.9% in-hospital death.

The cerebral hematoma volume is an important predictor of prognosis for patients with intracerebral haemorrhage. In our study, for each ml increase in initial haematoma volume the risk of in-hospital death increased by 4.8%. The value that is best oriented towards the risk of in-hospital death was 7.1 ml.

The irregular shape of the hematoma and the heterogeneous density, as defined by the Barras criteria, are independent predictors of death during hospitalisation.

The absolute density of the hematoma volume at admission is not an independent predictor of prognosis, but the density of hematoma at 3 days from the initial examination is

significantly associated with death during hospitalisation. For each HU unit increase in density at three days the risk of in-hospital death raises by 20%.

The imaging non-contrast signs associated with the risk of haematoma expansion were more frequent in patients who died during hospitalisation but these markers are not independent predictors of in-hospital death.

The absolute perihematic oedema volume was significantly greater in patients which died during hospitalisation compared to patients who survived, at admission as well as at 3 days ± 12 hours and 6 days ± 24 hours. However, it was not an independent predictor of in-hospital death.

The absolute volume of perihematic oedema at admission was an independent predictor of unfavourable prognostic after adjusting for the initial hematoma volume. For each ml increase in perihematic oedema the chances for a good prognosis drop by 9%.

The relative perihematic oedema had median values of 0.6 at hospital admission 1.7 at 3 days ± 12 hours from the initial evaluation, 2.5 at 6 days ± 24 hours from the initial evaluation, and 4.9 at 10 days ± 24 hours from the initial evaluation. The relative perihematic oedema was not an independent predictor of outcome during hospitalisation.

The median rate of perihematic oedema expansion at 3 days ± 12 hours was 30ml/h in the group of patients that died during hospitalisation as opposed to the group of patients that survived in which it was 0.09ml/h. Nevertheless, it was not an independent predictor of prognosis for patients with intracerebral haemorrhage.

The results obtained in our study can significantly contribute to the selection process of patients with intracerebral haemorrhage for different types of acute-phase therapies whose concrete benefit is influenced by factors that are as up no incompletely defined.

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