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Establishing reliable selection criteria for performing fibrinolytic therapy in patients with intracerebral haemorrhage based on prognostic tools

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ABSTRACT

Objectives: Minimally invasive surgery combined with fibrinolytic therapy is a promising treatment option for patients with intracerebral haemorrhage (ICH), but a meticulous patient selection is required, because not every patient benefits from it. The ICH score facilitates a reliable patient selection for fibrinolytic therapy except for ICH-4. This study evaluated whether an additional use of other prognostic tools can overcome this limitation.
Materials and Methods: A consecutive ICH patient cohort treated with fibrinolytic therapy between 2010 and 2020 was retrospectively analysed. The following prognostic tools were calculated: APACHE II, ICH-GS, ICH-FUNC, and ICH score. The discrimination power of every score was determined by ROC-analysis. Primary outcome parameters regarding the benefit of fibrinolytic therapy were the in-hospital mortality and a poor outcome defined as modified Rankin scale (mRS) > 4.
Results: A total of 280 patients with a median age of 72 years were included. The mortality rates according to the ICH score were ICH-0 = 0 % (0/0), ICH-1 = 0 % (0/22), ICH-2 = 7.1 % (5/70), ICH-3 = 17.3 % (19/110), ICH-4 = 67.2 % (45/67), ICH-5 = 100 % (11/11). The APACHE II showed the best discrimination power for in-hospital mortality (AUC = 0.87, $p < 0.0001$) and for poor outcome (AUC = 0.79, $p < 0.0001$). In the subgroup with ICH-4, APACHE II with a cut-off of 24.5 showed a good discriminating power for in-hospital mortality (AUC = 0.83, $p < 0.001$) and for poor outcome (AUC = 0.87, $p < 0.001$).
Conclusions: An additional application of APACHE II score increases the discriminating power of ICH score 4 enabling a more precise appraisal of in-hospital mortality and of functional outcome, which could support the patient selection for fibrinolytic therapy.

Introduction

Spontaneous intracerebral hemorrhage (ICH) is a subtype of stroke usually associated with chronic hypertension and/or amyloid angiopathy. Primary brain injury through tissue disruption and secondary brain injury due to edema formation contribute to a high in-hospital mortality following ICH and leave ICH survivors with a substantial disability.[1] After several randomized controlled trials failed to demonstrate an outcome benefit of surgical treatment, surgical interventions are currently performed on an individual level in clinical practice. Especially, the use of minimally invasive surgical approaches with endoscopic hematoma evacuation or fibrinolytic therapy applying recombinant tissue plasminogen activator (rtPA) increased in the past years attempting to reduce surgery-related brain injury. However, not every ICH patient benefits from fibrinolytic therapy, requiring a meticulous patient selection.[2] The rationale for performing surgical interventions is to significantly reduce the in-hospital mortality and morbidity while avoiding unnecessary operations in patients, who are not going to profit from surgery. Several prognostic tools have been developed for an early estimation of 30-day mortality and functional outcome in ICH patients, that can support the decision-making process, by identifying the patients, who will benefit from surgical treatment. The ICH score, as originally described by Hemphill et al. is one of the most frequently applied scores for early mortality estimation in ICH patients, that has also shown a good performance concerning the patient selection for fibrinolytic therapy.[3–5] While patients with ICH score 5

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were no candidates for fibrinolytic therapy, patients with ICH score 1-3 are eligible for fibrinolytic therapy and have higher chance of profiting from this surgical intervention. The prognosis estimation in patients with ICH score 4 was not as conclusive as the other ICH scores needing further clarification. The purpose of this study was to investigate whether the additional use of APACHE II (Acute Physiology and Chronic Health Evaluation), ICH-GS (ICH grading scale) or ICH-FUNC score (functional ICH score) can lead to a more reliable patient selection for fibrinolytic therapy, especially, in the subgroup with ICH score 4.

Methods

Study design and study population

This is a retrospective observational study including a consecutive patient cohort with spontaneous ICH treated by fibrinolytic therapy at our center in the time between 2010 and 2020. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the revised Helsinki Declaration of 1975.[6] Ethical approval (3/11/20) was granted by the local ethics committee of the University Medical Center Göttingen. Due to the retrospective study design, an informed consent was waived.

Calculation of prognostic scores

Clinical grading scales (ICH score, ICH-GS, ICH-FUNC score, and APACHE II score) were calculated for every patient.[4,7–10] The ICH score includes the following parameters: age (≤ 80 years= 0 vs. > 80 years= 1), hematoma volume (≤ 30 mL= 0 vs. > 30 mL= 1), intraventricular hemorrhage (no= 0, yes= 1), and initial clinical status according to the Glasgow Coma Scale (GCS) score (GCS 3–4= 2, GCS 5–12= 1, and GCS 13–15= 0). Since patients with infratentorial ICH do not receive fibrinolytic therapy, the range of the ICH score in our study was from 1 to 5. The ICH-GS (range 5-13) includes all parameters of the original ICH score, but applies different cut-off values: age (< 45 years= 1, 45-64= 2; ≥ 65 years= 3), hematoma volume (supratentorial: < 40 mL= 1, 40-70= 2, > 70= 3; infratentorial: < 10 mL= 1, 10-20 mL= 2, > 20 mL= 3), ICH location (supratentorial= 1, infratentorial= 2), initial clinical status according to GCS score (GCS 13-15= 1, GCS 9-12= 2; GCS 3-8= 3), and intraventricular hemorrhage (no= 1, yes= 2). The lower the value the better the prognosis.[7] The ICH-FUNC score is a functional outcome risk stratification scale (range 0-11) that includes age (< 70 years= 2 vs. 70-79 years= 1 ≥ 80 years= 0), hematoma volume (< 30 mL= 4 vs. 30-60= 2 vs. > 60 mL= 0), ICH location (lobar= 2, deep= 1, infratentorial= 0), initial GCS score (GCS ≥ 9= 2 vs. ≤ 8= 0) and pre-ICH cognitive impairment (no= 1, yes= 0). The APACHE II score (range 0-71) is based on 12 physiologic parameters (temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, white blood count, GCS, each with points from -3 to +3), the patients ́age (≤ 44: 0 points, 45–54: 2 points, 55–64: 3 points, 65–74: 5 points, ≥ 75: 6 points), and the previous health status (severe organ system insufficiency or immune-compromised assign, for nonoperative or emergency postoperative patients: 5 points, for elective postoperative patients: 2 points). The GCS was extracted from the emergency room protocol. If intubation or sedation was performed by the emergency physician, the state of consciousness prior to this intervention was used, which is additionally documented in the protocol. The scores and all data collections and evaluations relevant for the scores were calculated and done by Regina Schwiddessen and supervised by Vesna Malinova on a sample basis. The ICH volume was measured using the Brainlab® software and was based on the nonenhanced computed tomography 3D dataset. The ICH, that presents hyperdense on the CT scan, was easily segmented by means of the smart brush function providing the volume of the segmented hematoma in ml. Before starting the volumetric measurements, Regina Schwiddessen was trained by Vesna Malinova, who has an experience in using the Brainlab® software on a routine basis for more than 10 years. Since most parameters of the scores are clearly defined, we found no discrepancies in the evaluations performed by the two authors (R.S. and V.M.).

Outcome parameters

Primary outcome parameters were in-hospital mortality and functional outcome according to the modified Rankin scale (mRS) at discharge. A mRS > 4 was defined as poor outcome.

Statistical analysis

The statistical analysis was carried out using the statistics software GraphPad Prism Version 7.0. / IBM SPSS Statistics Version 28.0. A descriptive analysis was performed to present patient characteristics. The normal distribution was examined using the Kolmogorov-Smirnov test. Differences were calculated by using the chi-square test, the Fisher exact test or Mann-Whitney-U-test as appropriate. Since there was no normal distribution for the Apache II score ($p < 0.001$), the Mann-Whitney-U-test as a non-parametric test method was used and the median was determined. A p-value ≤ 0.05 was considered statistically significant when interpreting the results by using two-sided tests. Receiver operating characteristics curve (AUROC) statistics were performed to assess the discrimination of the individual scores.

Role of the funding source

There was no funding source for this study.

Results

A total of 280 patients were analyzed, 129 patients (46.1 %) were female, and 151 patients (53.9 %) were male. The median age of the study population was 72 [IQR= 63-79] years. The mean initial hematoma volume was 55.59 ± 27.61. In 150 patients (53.6 %) the hematoma was deep-seated, and 130 patients (46.4 %) had a lobar hematoma. All patients had a supratentorial ICH. The patient characteristics are summarized in Table 1.

The in-hospital mortality rate was 28.6 % (80/280). The median ICH score in the study population was 3 (IQR= 2–4). A higher ICH score was associated with the in-hospital mortality ($p < 0.0001$) and with poor outcome ($p < 0.001$). The in-hospital mortality rates and the number of patients with poor outcome dependent on the ICH score are shown in Table 2. The median ICH-FUNC score was 5 (IQR= 4–6). A lower ICH-FUNC score was associated with the in-hospital mortality ($p < 0.0001$) and with poor outcome ($p < 0.0001$). The median ICH-GS score in the study population was 9 (IQR= 8.25-10). A higher ICH-GS score was significantly associated with the in-hospital mortality ($p < 0.0001$) and with poor outcome ($p < 0.0001$). The median APACHE II score in the study population was 20 (IQR= 19–22). ICH survivors had a significant lower score ($p < 0.0001$) than the patients who died. Patients with good outcome at discharge had a significant lower score than those with poor outcome ($p < 0.001$). The in-hospital mortality rates dependent on the prognostic scores are summarized in Table 2. All prognostic scores showed a good discrimination power for in-hospital mortality and outcome (Table 3). The APACHE II had the best discrimination power with AUC of 0.87 for in-hospital mortality and AUC of 0.79 for poor outcome ($p < 0.0001$). In the subgroup with ICH score 4, the APACHE II score with a cut-off of 24.5 allowed a good discrimination concerning in-hospital mortality (AUC= 0.83, $p < 0.001$) and outcome (AUC= 0.87, $p < 0.001$) (Figs. 1 and 2). The Grotta bars (Fig. 3) clearly show that a greater proportion of patients with ICH score 4 and an APACHE II score ≥ 24.5 have worse values on mRS at discharge than patients with an APACHE II score < 24.5.

Table 1
Patient characteristics.

Parameters (n= 280)	
Age, years, median [IQR]	72 [63-79]
Age [Categorized as in the scores]	% (n)
Categorization based on ICH score	
≥80 years	23.2 % (65/280)
<80 years	76.8 % (215/280)
Categorization based on ICH-FUNC score	
<70	43.6 % (122/280)
70-79	33.2 % (93/280)
≥ 80	23.2 % (65/280)
Categorization based on ICH-GS	
< 45	5.0 % (14/280)
45-64	23.9 % (67/280)
≥ 65	71.1 % (199/280)
Gender	
Male	53.9 % (151/280)
Female	46.1 % (129/280)
GCS, mean ± SD	8.88±3.63
GCS [Categorized as in the scores]	% (n)
Categorization based on APACHE II score	
GCS 3	13.6 % (38/280)
GCS 4	10.0 % (28/280)
GCS 5	2.5 % (7/280)
GCS 6	2.1 % (6/280)
GCS 7	1.8 % (5/280)
GCS 8	8.9 % (25/280)
GCS 9	6.4 % (18/280)
GCS 10	11.4 % (32/280)
GCS 11	12.9 % (36/280)
GCS 12	18.9 % (53/280)
GCS 13	5.4 % (15/280)
GCS 14	3.2 % (9/280)
GCS 15	2.9 % (8/280)
Categorization based on ICH score	
GCS 3-4	23.6 % (66/280)
GCS 5-12	65.0 % (182/280)
GCS 13-15	11.4 % (32/280)
Categorization based on ICH-FUNC score	
GCS ≥ 9	61.1 % (171/280)
GCS ≤ 8	38.9 % (109/280)
Categorization based on ICH-GS	
13-15	11.4 % (32/280)
9-12	49.6 % (139/280)
3-8	38.9 % (109/280)
IVH, n (%)	60.4 % (169/280)
Hematoma volume, mean ± SD	55.59±27.61
Hematoma volume [Categorized as in the scores]	% (n)
Categorization based on ICH score:	
≥30 mL	84.6 % (237/280)
<30 mL	15.4 % (43/280)
Categorization based on ICH-GS [supratentorial ICH]	
< 40 ml	31.8 % (89/280)
40-70 ml	45.7 % (128/280)
>70 ml	22.5 % (63/280)
Hematoma localization, n (%)	
Deep	53.6 % (150/280)
Lobar	46.4 % (130/280)
Pre-ICH-cognitive impairment	0 % (0/280)
In-hospital mortality	80 (28.6 %)
mRS at discharge	4.5 [IQR 4-6]
GOS at discharge	3 [IQR 1-3]

Data are mean with ± standard deviation, median [interquartile range], % (n), n= 280.

Discussion

The clinical decisions for surgical treatment of patients with ICH are currently made on an individual basis, because none of the conducted randomized controlled trials was able to show a benefit concerning the outcome after surgical hematoma evacuation.[11–13] While no significant improvement of functional outcome has been achieved in a large recently published randomized controlled trial evaluating fibrinolytic therapy (MISTIE III), some ICH patients seemed to benefit from this treatment. On the other hand, the initial prognostic uncertainty often leads to unnecessary surgical interventions without benefit for the patient resulting in severe disability, that does not reflect the declared patient will. Hence, a meticulous patient selection is required emphasizing the need of defining clear selection criteria for surgery in this patient cohort.[2,11] Several prognostic tools have been developed for the assessment of mortality and functional outcome after ICH.[4,5,7–10,14] A recently published systematic review provides a summary of existing prognostic tools with critical regard concerning the validity of these tools due to a lack of validation studies.[14] The primary goal of establishing such prognostic tools for ICH patients is to guide the clinical decision-making and not to exactly predict the outcome of the patients. The consideration of the individual patient's will also plays an important role during the decision-making process concerning the extent of therapeutic measures and the indication for performing surgical interventions for treatment ICH, which is in line with the current discussion in the literature.[15,16] Consequently, by combining the scores and use them for predicting mortality and morbidity, we did not pursue a goal of providing an exact forecast, but to create a risk-stratification tool for the decision-making process. Another problem that needs to be addressed is the lack of unified cut-off values for the parameters considered by different prognostication tools. Additionally, a heterogeneity exists concerning the evaluated patient populations regarding the received treatment either including only patients with conservative treatment or patients undergoing surgical treatment and, therefore, impeding a uniform implementation of these scores in clinical practice.[17–19] In a recently published study, a high predictive value of functional outcome at 90 days follow-up was found for NIHSS, age, volume of the hematoma, and presence of IVH for the outcome

Table 2
Mortality and bad functional outcome in dependence of the different scores.

Scores	n (%)	In-hospital mortality	Poor outcome (mRS 5-6)
ICH Score			
0	0	0/0	0
1	22 (7.9 %)	0/22	2/22 (9.1 %)
2	70 (25 %)	5/70 (7.1 %)	24/70 (34.3 %)
3	110 (39.3 %)	19/110 (17.3 %)	49/110 (44.5 %)
4	67 (23.9 %)	45/67 (67.2 %)	54/67 (80.6 %)
5	11 (3.9 %)	11/11 (100 %)	11/11 (100 %)
ICH-FUNC score			
0	0	0	0
1	0	0	0
2	10 (3.6 %)	10/10 (100 %)	10/10 (100 %)
3	42 (15 %)	27/42 (64.3 %)	34/42 (81 %)
4	62 (22.1 %)	23/62 (37.1 %)	41/62 (66.1 %)
5	53 (18.9 %)	13/53 (24.5 %)	26/53 (49.1 %)
6	81 (28.9 %)	6/81 (7.4 %)	19/81 (23.5 %)
7	32 (11.4 %)	1/32 (3.1 %)	10/32 (31.3 %)
8	0	0	0
9	0	0	0
10	0	0	0
11	0	0	0
ICH-GS			
5	0	0	0
6	2 (0.7 %)	0/2 (0 %)	1/2 (50 %)
7	31 (11.1 %)	1/31 (3.2 %)	5/31 (16.1 %)
8	37 (13.2 %)	1/37 (2.7 %)	12/37 (32.4 %)
9	71 (25.4 %)	15/71 (21.1 %)	32/71 (45.1 %)
10	70 (25 %)	17/70 (24.3 %)	37/70 (52.9 %)
11	47 (16.8 %)	27/47 (57.4 %)	34/47 (72.3 %)
12	22 (7.9 %)	19/22 (86.4 %)	19/22 (86.4 %)
13	0	0	0
APACHE II			
Survivor	200	18 [16-22]	18 [15-21]
Death	80	25 [23.5-29]	24 [20-27.75]

Data are mean with ± standard deviation, median [interquartile range], *N* (%), n= 280.

Table 3
Receiver Operating Characteristic for ICH score, ICH-FUNC score, ICH-GS and for APACHE II score, n=280.

Scores	ICH score 0-5				ICH score= 4			
	MORTALITY		POOR OUTCOME		MORTALITY		POOR OUTCOME	
	AUC	p-value	AUC	p-value	AUC	p-value	AUC	p-value
ICH score	0.84	<0.0001	0.74	<0.0001	0.5	1.0	0.5	1.0
ICH-GS	0.81	<0.0001	0.71	<0.0001	0.73	0.002	0.61	0.207
APACHE II	0.87	<0.0001	0.79	<0.0001	0.83	<0.001	0.87	<0.001
ICH-FUNC	0.82	<0.0001	0.75	<0.0001	0.72	0.003	0.73	0.012

n= 280.

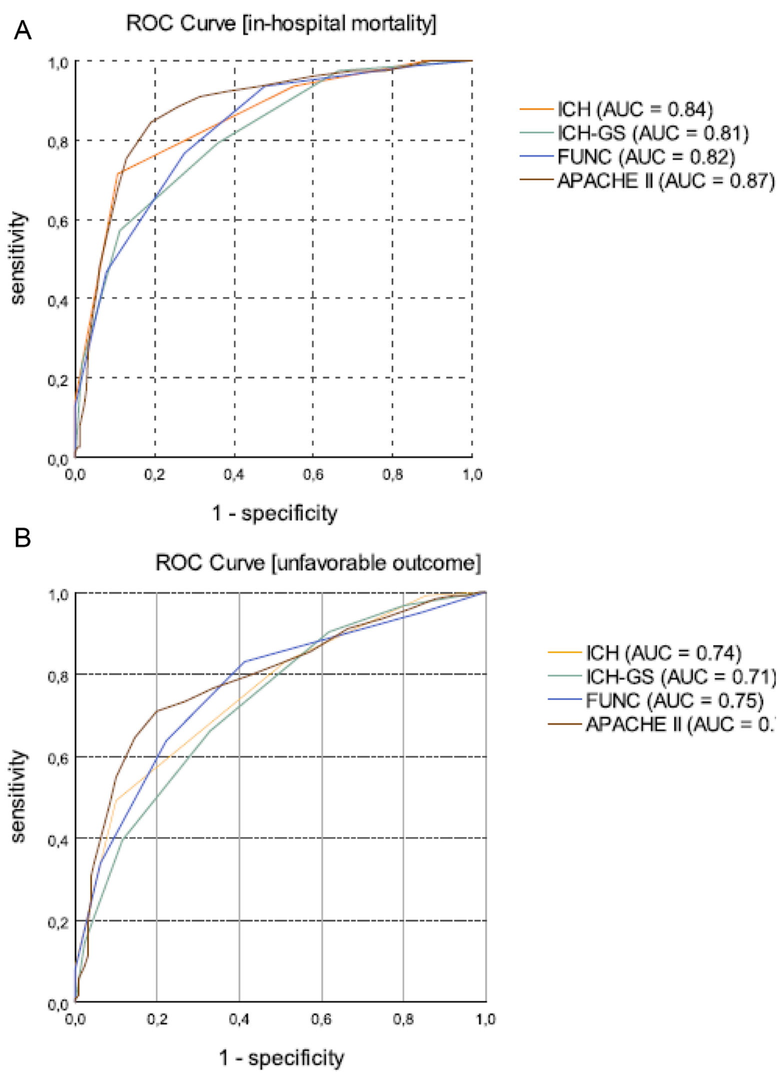

Fig. 1. ROC Curves in patients with ICH score 1-5 for predicting in-hospital mortality (A) and unfavorable outcome (B), n= 280.

prediction of ICH patients receiving only conservative treatment.[17] However, these findings cannot be automatically transferred to ICH patients undergoing fibrinolytic therapy. Considering the fact of potentially improved outcomes through surgical procedures, Zyck et al. assumed a possible overestimation of the risk for poor outcome by applying the prognostic tools in these patient populations and recommended a separate evaluation of the scores in patient cohorts with ICH receiving different surgical treatments.[18] Our study contributes to increased evidence about the usefulness of these prognostic tools for risk-stratification during the clinical decision-making process considering the indication for fibrinolytic therapy in patients with ICH.

The treatment goals, that would justify fibrinolytic therapy are: 1-prevention of in-hospital mortality; and 2-survival with minimal morbidity and a probability of improvement during rehabilitation, defined as mRS $\leq$ 4 at discharge. A mRS $\leq$ 4 was considered good outcome at discharge in our study, since this was deemed a realistically achievable outcome with the possibility of functional recovery after rehabilitation. Hemphill et al. demonstrated that conservative treated ICH patients with a score of 4 at discharge remained the same or improved their functional status and patients with a mRS of 5 reached a maximum mRS of 4 in the follow-up period or have worsened, thus we defined the cut-off value for a good outcome at discharge at mRS $\leq$ 4.[5] Patients with ICH seem to have the potential for recovery during rehabilitation if they survive the initial bleeding event.[20] Gordillo et al. have

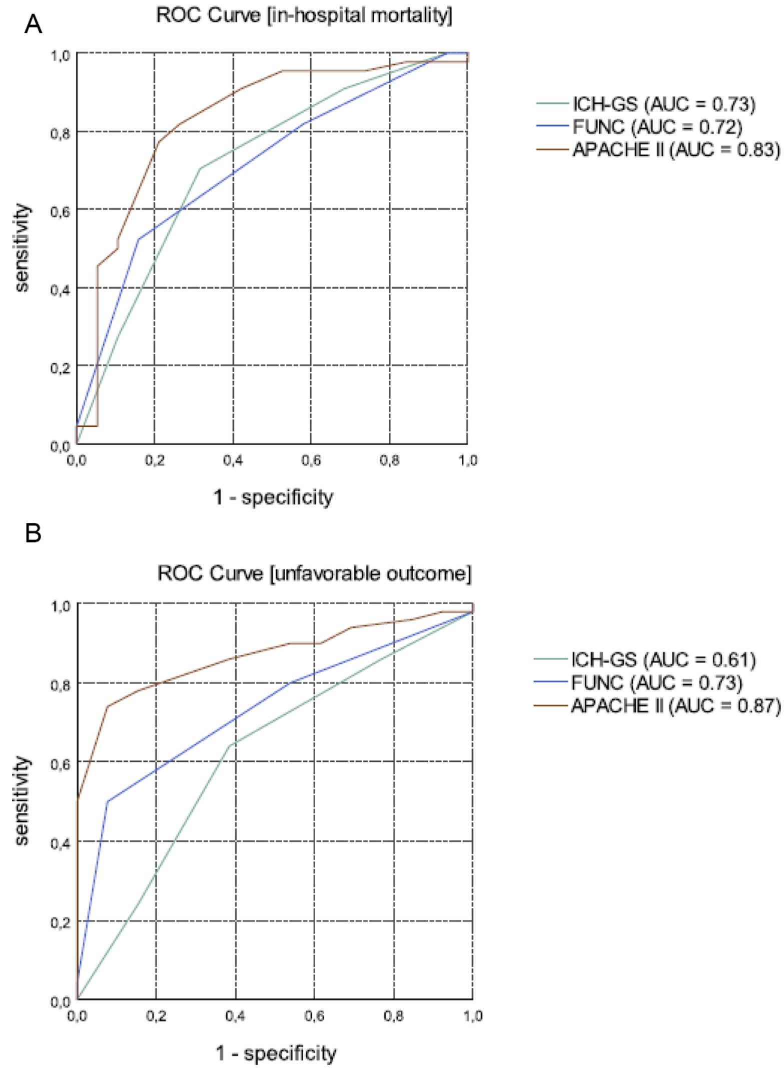

Fig. 2. ROC Curves in patients with ICH score 4 for predicting in-hospital mortality (A) and unfavorable outcome (B), n= 280.

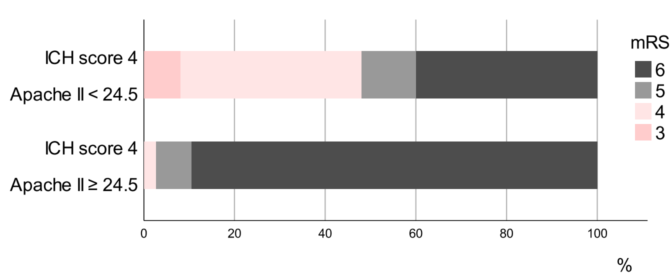

Fig. 3. mRS-Grotta bar for patients with ICH score 4 and an Apache II score ≥ 24.5 versus < 24.5.

shown further improvement in functional status of ICH patients after six months, one year, and five years. Thus, the risk stratification scores should not be used to predict a good outcome upon discharge, but rather to estimate the outcome that can serve as the basis for subsequent recovery. The focus only on short-term outcomes may lead to discontinuation of treatment even though the chances of recovery and of achieving a long-term acceptable condition appear to be high if the patient survives the event.[21] This must be considered during the treatment decision-making in diseases such as ICH with a known high mortality and short-term morbidity.

The widely used ICH score facilitated a conclusive prognosis estimation for ICH patients undergoing fibrinolytic therapy with ICH score 1, 2, 3 and 5.[3–5] While patients with ICH score 1, 2 and 3 had a clear benefit from fibrinolytic therapy, patients with ICH score 5 had an in-hospital mortality rate of 100 % despite fibrinolytic therapy, hence, patients with ICH score 5 should not be considered suitable candidates for fibrinolytic therapy. Unlikely, the discriminatory power of ICH score 4 was not as much decisive as the other scores. The in-hospital mortality rate of patients with ICH score 4 was 43 %, while 57 % had benefited from fibrinolytic therapy. In this study, known prognostic tools were compared regarding their capability to reliably predict in-hospital mortality and morbidity in ICH patients treated with fibrinolytic therapy to answer the question whether they are suitable selection tools for indicating fibrinolytic therapy. The additional use of the well-established APACHE II score[10] for mortality estimation in critically ill patients at the intensive care unit was able to increase the discriminatory power in the patient subgroup with ICH score 4. APACHE II score with a cut-off value of 24.5 showed good discrimination power for mortality as well as for functional outcome. Two previously published studies have shown that the APACHE II score can be used to forecast mortality of ICH patients, our study was the first, focusing on fibrinolytic treated ICH patients and considering mortality as well as functional status as outcome parameters.[22,23] The combination of the ICH score and the APACHE II score ≥ 24.5 was associated with fatal prognosis in our study population. According to this finding, patients with these scores have a high probability, but not certainty of dying in the hospital. The use of these scores should support the decision-making process in clinical practice but cannot replace a critical weighing up of pros and cons by the treating physician. Additionally, the patients' personal preferences should be considered during the final decision-making for conducting fibrinolytic therapy. The combined use of both scores (ICH score and APACHE II score) needs an external validation to confirm the findings of our study cohort. However, the high discrimination power of the APACHE II score, a score strongly influenced by physiological parameters, suggests, that systemic body reactions after brain tissue damage such as inflammation, fever or an increase of white blood cell count are relevant for outcome, as already shown for ICH patients.[22,24–27] Thus, not only stroke-specific parameters but also general disease severity classification systems should be considered for prognosis estimation. Further two prognostic tools focusing on functional outcome after ICH (ICH-FUNC and ICH-GS) were also included in the analysis of this study. Even though the ICH-GS and the ICH-FUNC were able to forecast both outcome parameters after fibrinolytic therapy in ICH patients, none of them was able to predict it comparable to the APACHE II score. Considering the findings of our study, rather, the consideration of the systemic reaction as reflected by the APACHE II score added the most to the prognostic value of the ICH score as a selection criterion for fibrinolytic therapy in ICH patients. Based on our findings, the initial use of the ICH score is recommended; in the case of an ICH score of four, which is associated with an uncertain prognosis, the additional use of the APACHE II score could ensure a more detailed patient selection.

Limitations of the study

The retrospective study design is the main limitation of the study. Especially in calculating the APACHE II score, for which a lot of data and a complex calculation is necessary, errors cannot be completely excluded. A disadvantage of the APACHE II score is the complex data collection and score calculation as well as the collection time over a 24-h period. Regarding daily clinical routine the time-consuming calculation needs a consideration. The impact of withdrawal on mortality and on outcome estimation should also be considered because it is associated with an increasing mortality rate.[28]

Conclusion

In summary, the ICH score should be used as a simple and quick assessment tool in the acute setting for initial patient selection. The more detailed and complex to calculate APACHE II score should be added in patients with initially inconclusive risk stratification. While ICH score facilitates a risk stratification-based decision-making in ICH patients with ICH 1, 2, and 3 receiving fibrinolytic therapy, this is not as much decisive in the subgroup of patients with ICH score 4. Patients with ICH score 5 had a mortality rate of 100 % despite fibrinolytic therapy and don't seem to be suitable candidates for fibrinolytic therapy. An additional calculation of APACHE II score with a cutoff value of 24.5 in this subgroup increases the discriminating power enabling a more precise appraisal of mortality and outcome, which may be supportive during the selection of patients for fibrinolytic therapy.

Department and institution where work was performed

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CRediT authorship contribution statement

Regina Schwiddessen: Writing – original draft, Investigation, Formal analysis, Methodology, Data curation, Conceptualization, Visualization. **Christian von der Brelie:** Writing – review & editing, Methodology, Conceptualization. **Dorothee Mielke:** Writing – review & editing. **Veit Rohde:** Writing – review & editing, Supervision. **Vesna Malinova:** Project administration, Writing – review & editing, Investigation, Formal analysis, Methodology, Data curation, Conceptualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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