HEART RATE ENTROPY IS ASSOCIATED WITH MORTALITY AFTER INTRACEREBERAL HEMORRHAGE

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Abstract

Background: Autonomic nervous system changes have been associated with outcome after intracerebral hemorrhage (ICH) previously. We aimed to investigate the association of heart rate entropy (HRE) with mortality after ICH. **Methods:** Sample HRE, hear rate variability and baroreflex sensitivity were examined in consecutive ICH patients. Hematoma volume, intraventricular hemorrhage, infratentorial origin, consciousness impairment and age were combined into standard ICH score. **Results:** In 47 patients suffering ICH (mean age 61 years, median hemorrhage volume 38 mL) the areas under the curve (AUC) for mortality were 0.86, 0.83, 0.76, 0.74, 0.72 and 0.7 for HRE, ICH-score, normalized low frequency powers, low frequency/high frequency powers ratio, normalized high frequency powers and BRS, respectively. HRE and ICH score were associated with mortality independently (adjusted odd ratio (aOR) 0.09, 95% confidence interval (CI) 0.1-0.8, p=0.03 and aOR 2.6, CI 1.03-6.6, p=0.04). Combining ICH score with HRE into a novel score resulted in an AUC of 0.94, CI 0.88-0.99, p<0.001. **Conclusion:** Compared to several autonomic markers HRE seems to bear the largest amount of information on death probability after ICH. Moreover, HRE may predict mortality comparable to ICH score. Combining HRE with ICH score may increase the predictive performance for mortality after ICH.

Background

Changes in the cardiovascular regulations mediated by autonomic nervous system (ANS) reflect acute reaction to the pathological state. Measures of ANS activity as heart rate variability (HRV) and baroreflex sensitivity (BRS) have been shown previously to be associated with mortality and functional outcome following stroke including ICH. [1-3] Heart rate entropy (HRE) is as a non-linear method mirroring complexity in the signal behaviour of heart rate intervals.[4] Regulation of the heart rate by the ANS is thought to be a complex biological system. Complex systems are the one that are very sensitive to initial conditions and reacts adaptively to minute changes in its environment. Therefore, the complexity of such a system can be directly correlated to its ability to adapt to change and hence logically, when this ability is lost, the complexity of the system is also adversely affected. The loss of complexity behaviour may therefore be indicative of pathological changes in the underlying autonomic cardiovascular regulations. Analysis of entropy is a non-linear concept used to describe system randomness or unpredictability. Entropy is originally a physical term. According to third principle of thermodynamics, entropy of universe increases uniformly to infinity, as most of physical processes are irreversible. In terms of heart rate, entropy is a synthetic index of heart rate control. High entropy indicates multiple loops of heart rate control working simultaneously according to the body needs. Decreasing control (for example absolutely dominant respiratory arrhythmia commonly seen after brain-stem death) is mathematically expressed with low entropy. *Approximate entropy* has been proposed as a measure of irregularity of time series of various origins.[5] It quantifies the predictability of subsequent amplitude values of data series based on the knowledge of the previous ones; the less the predictability the larger the approximate entropy. However, these calculations

classically require very long data sets and a bias may exist leading to overestimation of the time series regularity. *Sample entropy* addresses this problem to an extent.[4] Heart rate entropy has been successfully utilized to predicts outcome after trauma [6] or cardiac arrest [7] however, data on intracerebral haemorrhage is scarce.[8] We hypothesized that HRE may harbour information on mortality following ICH that is superior to established measures of ANS including HRV and BRS and comparable to standard clinical scores as e.g. the ICH score.[9]

Methods

Population

Patients with ischemic and haemorrhagic stroke fulfilling criteria for unbiased autonomic measurement were collected in a prospective database reported previously.[10,11] Briefly, this database included consecutively admitted acute stroke patients free of previous stroke, diabetes mellitus, myocardial infarction, chronic renal failure, or other medical conditions known to affect autonomic functions. Patients with atrial fibrillation and cardiac pacemakers were excluded. Chronic antihypertensive medication was allowed and documented. For the purposed of the currents study we retrospectively analysed patients who fulfilled following criteria: 1) acute intracerebral haemorrhage as diagnosed by CT or MRI; 2) at least 5 min artefact free continuous beat-to beat blood pressure recording within the first 24 h after symptoms onset; and 3) freedom from acute antihypertensive treatment before or upon admission. Patient with do-not-resuscitate (DNR) orders were excluded.

Assessment of autonomic functions

Blood pressure for assessment of autonomic functions was measured noninvasively using the Finometer device (FMS, Finapres Medical Systems BV, Amsterdam, Netherlands). This device employs a volume clamp method to capture beat-to-beat (continuous) values of blood pressure and pulse rate in the finger artery. A cuff of appropriate size was attached to the middle finger of the non-hemiparetic hand of the patient in supine position and the hand was maintained at heart level. Using the Finometer device, continuous blood pressure and pulse rate for autonomic assessment was recorded within 24 h after stroke onset, usually directly upon admission, after 30 min of resting in a separated, closed, and quiet room, for a period of 10 min. No serial measurements were performed. The ICM+® software (Cambridge Enterprise Ltd, Cambridge, UK, https://icmplus.neurosurg.cam. ac.uk) was used for the retrospective analysis of stored Finometer signals. According to the international guidelines on HRV analysis,[12] we calculated parameters from the frequency domain analysis. For all HRV parameters we used 300 s time series of continuous blood pressure signal. The raw data, recorded originally at sampling rate of 100 Hz were up-sampled to 200 Hz and processed through a peak detection algorithm based on Pan-Tomkins method.[13] Artefacts like device calibration as well as individual ectopics were automatically removed prior to further analysis. Sample Entropy of the beat-to-beat heart cycle period time series was calculated according to the algorithm described by Richman and Moorman. [4] In brief, sample entropy estimates the likelihood that two similar sequences of m consecutive data points (here m = 2) will remain similar when the sequence length increases to m + 1 data points. It is computed as the negative natural logarithm of the ratio of number of m + 1 length patterns to the number of corresponding m length patterns. That is higher

Sample Entropy values signify higher irregularity of the time series. Lomb-Scargle periodogram, suitable for analysis of irregularly sampled data, was used to calculate spectral power of the same beat-to-beat time series in the very low frequency range (VLF: 0.003–0.04 Hz), low frequency range (LF: 0.04–0.15 Hz), the high frequency range (HF: 0.15–0.4 Hz), the total power (TP: 0.003–0.4 Hz) and the LF/HF ratio. Further, for HF and LF, normalized powers (HF/(TP–VLF) x 100 and LF/(TP–VLF) × 100, respectively) were calculated. BRS was calculated by using a modification of the sequential cross-correlation method. [14] The modified function uses ABP systolic peaks to create beat-to-beat (BB) interval time series, by using an automated detection algorithm. The slope of the linear regression between 10-second series of BB intervals and the corresponding 10-second series of systolic blood pressure is then calculated. In order to remove the influence of an unknown time delay of the baroreceptor response, a cross-correlation function is used to maximize the correlation coefficient. The BB intervals window is shifted against the systolic pressure window in a stepwise manner; the highest correlation is reported if it fulfills the criteria outlined next. In order to ensure that the correlation calculations are always performed on the same number of data points irrespective of the lag applied to BB intervals series, the actual data buffer is extended with each window shift. A valid BRS value is returned only if the correlation coefficient is significant at a p value of less than 0.01, and if no irregular beats (ectopics) are detected by the software. To compensate for the influence of uncorrelated noise, the slope returned is adjusted (divided by) to the correlation coefficient. The BRS is updated every 10 seconds and expressed in ms/mm Hg.

Assessment of clinical and radiological parameters and the ICH score

Clinical severity at admission was scored according to the National Institute of Heath Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS). Demographic, baseline clinical and laboratory parameters including age, sex, history of hypertension, previous antihypertensive therapy, admission blood pressure, were recorded. Mortality at 90 days was retrieved using a standardized telephonic interview. The diagnosis of ICH was confirmed by CT or MRI. The ICH volume was calculated from the first CT or MRI scan using the a x b x c x 0.5 method for regular shapes and a x b x c x 0.33 for irregular shapes.[15,16] The presence of intraventricular hemorrhage extension (IVH) was recorded as present of absent. To take account and adjust for most relevant clinical and radiological factors, the „standard“ ICH score was calculated for each patient as previously described.[9] Shortly, ICH score consists of items including Glasgow Coma Scale (GCS) score at admission, age, initial hematoma volume, presence of IVH and infratentorial versus supratentorial origin. It represents an established composite marker combining clinical and radiological features to predict mortality. Each increase in the ICH score is associated with a progressive increase in mortality.

Statistics

Distribution of the data was visualized using histograms and tested using the one-sample Kolmogorov-Smirnov test. For normally distributed data the results are presented as mean, range, and standard deviation, for non-normally distributed data as median, range, and interquartile range. For comparison between the groups Fisher´s test, Mann-Whitney test, or Student´s unpaired *t*- test was used, as appropriate. To adjust for clinical and radiological variables, standard ICH score was

calculated and entered as co-variate into a logistic regression model. To examine and compare the prediction capabilities of ICH score and autonomic parameters receiver operating curve (ROC) and area under curve (AUC) were calculated. For the development of a novel score, first optimal predictive cut-off of HRE was calculated using Youden index and then the dichotomized HRE was combined with the standard ICH score using weights from the respective logistic regression model. Again, performance of scores were compared using ROC, AUC and De Long test. All statistics was performed using SPSS (Version 26, IBM) and MedCalc.

Ethics

The local ethics committee approved the study. All patients or their next of kin gave written informed consent.

Results

Population

47 patients with acute intracerebral haemorrhage fulfilled the inclusion criteria and entered the analysis. The mean age was 61 years and 42.6% were females. Median admission NIHSS was 13 points, median GCS 14 points, median haemorrhage volume was 38 ml and 55% had intraventricular extension of the haemorrhage (IVH). Median ICH score was 2 points. 60% of the patients underwent mechanical ventilation and 28% received surgical therapy. The mortality at 3 months was 12 (25.5%), see Table 1.

Associations of autonomic parameters and mortality at 3 months

In the univariate analysis patients dead at 3 months showed upon admission significantly lower normalized powers of LF band, higher normalized power of HF band, lower LF/HF ratios, lower baroreflex sensitivity and lower sample entropy of HR (HRE), see Table 2. The prediction capability the ICH score and autonomic parameters including HRE was calculated and compared using ROCs and AUCs. ICH-score and HRE displayed the largest AUCs, see Table 3. The difference between AUCs of ICH-score and HRE was not significant (AUC Difference 0.03, CI -0.15-0.21, p=0.7). In a multivariate logistic regression model HRE and ICH score predicted mortality independently (adjusted odd ratio (aOR) 0.09, 95% confidence interval (CI) 0.1-0.8, p=0.03 and aOR 2.6, CI 1.03-6.6, p=0.04). ROC of HRE was explored for cut-off point using the Youden score and dichotomized accordingly. Combining ICH score with dichotomized HRE into a novel score (ICH-HRE score, Table 4) resulted in AUC of 0.94, CI 0.88-0.99 outperforming the original ICH score (AUC Difference 0.12, CI 0.018- 0.22, p=0.02). For death probabilities according to ICH score and ICH-HRE score see Figure 1.

Discussion

Surrogates of autonomic nervous system activity in pathological conditions as intracerebral haemorrhage seems to carry information on disease severity and future outcome including survival or mortality. As systems underlying multilevel interactions of central autonomic regulations behave in highly complex and non-linear manner, we suggest that heart rate entropy may bear informational amount that is superior to established measures of autonomic nervous system as HRV and BRS. Decreased entropy of the heart rate may indicate loss of signal behaviour complexity due to

impaired cardiovascular regulations. Our observation is in line with previous reports. Tang et al. reported higher heart rate entropy levels in mixed stroke patients requiring ICU to be associated with favourable outcome. However, separate analysis for mortality and/or intracerebral haemorrhage was not shown. Chen et al. suggested borderline association between HRE and functional outcome in patients with intracerebral haemorrhage. Both studies used estimates of multiscale entropy (MsEn). In contrast, we used sample size entropy (SaEn) due to the short recordings. MsEN requires a lot longer buffers, as it calculates sample entropy on progressively more coarse grained data. MSEn performs better at recognising truly irregular and complex series as opposed to purely random ones. In contrast, SaEn may overestimate complexity in some cases. However, it does seem to be sensitive to *loss* of complexity, e.g. in pathological conditions. Associations between changes in the complex activity of the ANS and outcome after stroke or brain injury have been described previously. Underlying mechanisms remain speculative and may include broad range of phenomena as direct damage to the central autonomic network, sympathetic and parasympathetic overdrive and/or malfunction, impaired regulatory continuum between ANS and cerebral autoregulation and possible cardiac, metabolic, thromboembolic and infectious sequelae. [17-20] Certain limitations of our study have to be stressed. Due to the criteria for unbiased autonomic measurement, we excluded patients with previous stroke, myocardial infarction, atrial fibrillation, diabetes mellitus or other conditions known to affect autonomic functions as well as patients with active or acute antihypertensive treatment, producing thus a selection bias. This bias may limit a clear translation of our results into the general ICH population. Unfortunately, broad exclusion criteria for unbiased autonomic measurement are also responsible for the small sample size. This limits further

analyses on the association of HRE and hematoma localizations or medical interventions. Finally, while this was an retrospective analysis, we used for the derivation of heart rate intervals continuous arterial blood pressure (ABP) signal from the Finometer® device as the standard ECG signal was originally not recorded. Review of the literature comparing HRV parameters derived from ECG and ABP signals indicates overall sufficient comparability. [21] Summarizing all together, our results have to be interpreted with caution and regard to the above mentioned limitations. Interpretations and in particular the proposed novel score are thought to be mainly hypothesis generating.

Conclusion

Compared to several autonomic markers HRE seems to bear the largest amount of information on death probability after ICH. Moreover, HRE may predict mortality after ICH comparable to the ICH score. Combining HRE with ICH score may increase the predictive performance for mortality after ICH. This may be of clinical importance for future prediction and monitoring models.

Conflict of interest: None

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Disclosures: None

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Table 1. Demographic and clinical characteristics of the study population.

Variable	ICH, n=47
Age, mean (range, SD)	60.8 (17-86, 16.5)
Sex, n (%) females	20 (42.6)
History of hypertension, n (%)	35 (74.5)
Etiology	
Hypertension, n (%)	31 (66.0)
Amyloid angiopathy, n (%)	4 (8.5)
Arteriovenous malformation, n (%)	5 (10.6)
Coagulopathy, n (%)	3 (6.4)
Other, n (%)	2 (4.3)
Unknown, n (%)	2 (4.3)
Location	
Deep n (%)	30 (63.8)
Lobar n (%)	15 (31.9)
Pons n (%)	2 (4.3)
Admission NIHSS, median (range, IQR)	13.0 (2-34.0, 29.0)
Admission GCS, median (range, IQR)	14 (3-15, 13)
Hemorrhage volume, median (range, IQR)	37.7 (1.0-234.0, 56.1)
Intraventricular extension, n (%)	26 (55.3)
Mechanical ventilation, n (%)	28 (59.6)
Surgical therapy, n (%)	13 (27.7)
ICH score	2 (0-4, 2.0)
Mortality at 3 months, n (%)	12 (25.5)

SD – standard deviation, NIHSS – National Institute of Health Stroke Scale, IQR – interquarter range, GCS – Glasgow Coma Scale, ICH score[9]

Table 2. Univariate associations of autonomic markers with mortality at 3 months.

Variable	Alive at 3 months N=35	Dead at 3 months N=12	p
ICH score, points, median (range, IQR)	1.0 (0-2; 2.0)	3.0 (1-4; 1.75)	0.001
LF norm, median (range, IQR)	22.2 (5.1-52.2, 12.13)	14.7 (4.4-36.8, 10.44)	0.006
HF norm, median (range, IQR)	27.9 (10.8-82.6, 19.6)	39.1 (19.6-80.3, 27.5)	0.043
LF/HF ratio, median (range, IQR)	0.82 (0.10-4.13, 1.16)	0.40 (0.05-1.01, 0.60)	0.022
BRS, ms/mm Hg, median (range, IQR)	6.8 (0.73-49.13, 6.03)	4.01 (1.43-12.6, 6.01)	0.040
HRE, median (range, IQR)	2.15 (1.02-5.48, 0.95)	1.34 (0.99-2.33, 0.40)	<0.001

ICH score[9], LF norm- normalized power of the low frequency band, HF norm- normalized power of the high frequency band, BRS – baroreflex sensitivity, HRE –heart rate entropy.

Table 3. Predictions of mortality by AUCs for ICH score and autonomic markers.

Variables	AUC/ *1- AUC	Std.Error	p	95% Confidence Interval	
HF norm	0.72	0.089	0.027	0.54	0.89
LF norm*	0.76	0.86	0.008	0.59	0.93
LF/HF ratio*	0.72	0.082	0.023	0.56	0.88
BRS*	0.72	0.097	0.040	0.51	0.89
HRE*	0.86	0.066	<0.001	0.73	0.99
ICH-score	0.83	0.064	<0.001	0.70	0.95

AUC – area under curve, LF norm- normalized power of low frequency band, HF norm- normalized power of high frequency band, BRS – baroreflex sensitivity, HRE –heart rate entropy. The AUC values for variables marked with an asterix are shown as 1-AUC.

Table 4. Standard ICH-score and ICH-entropy score.

Item	ICH score (points)	ICH-entropy score (points)
GCS score 3-4 5-12 13-15	 2 1 0	 2 1 0
ICH volume (cm^3) ≥ 30 < 30	 1 0	 1 0
IVH Yes No	 1 0	 1 0
Age (years) ≥80 <80	 1 0	 1 0
Heart rate entropy ≤ 1.5 > 1.5		 1 0
Total score	0-5	0-6

GCS - Glasgow Coma Scale, ICH volume- hematoma volume, IVH – intraventricular hemorrhage

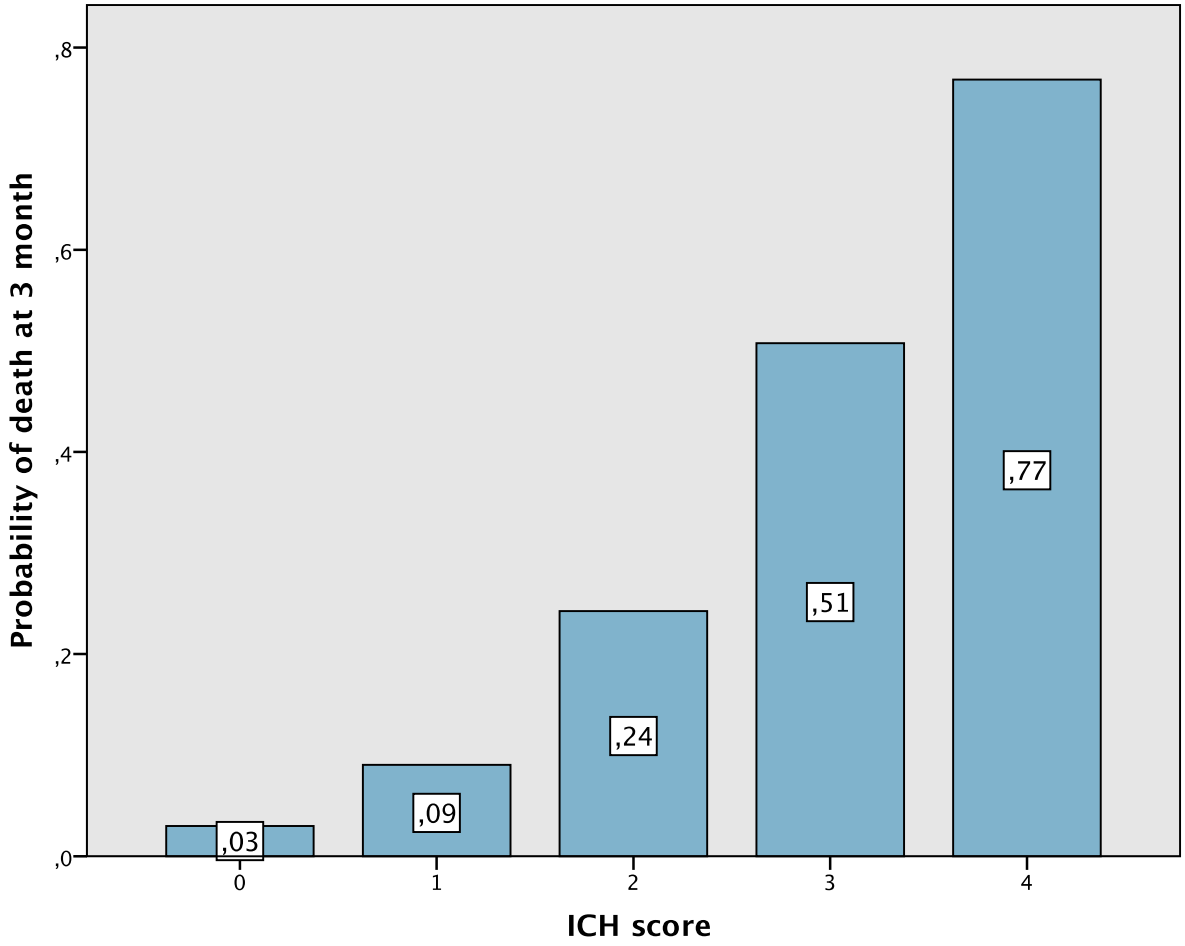

Figure 1. Probability of ICH-related death at 3 months by ICH-score.

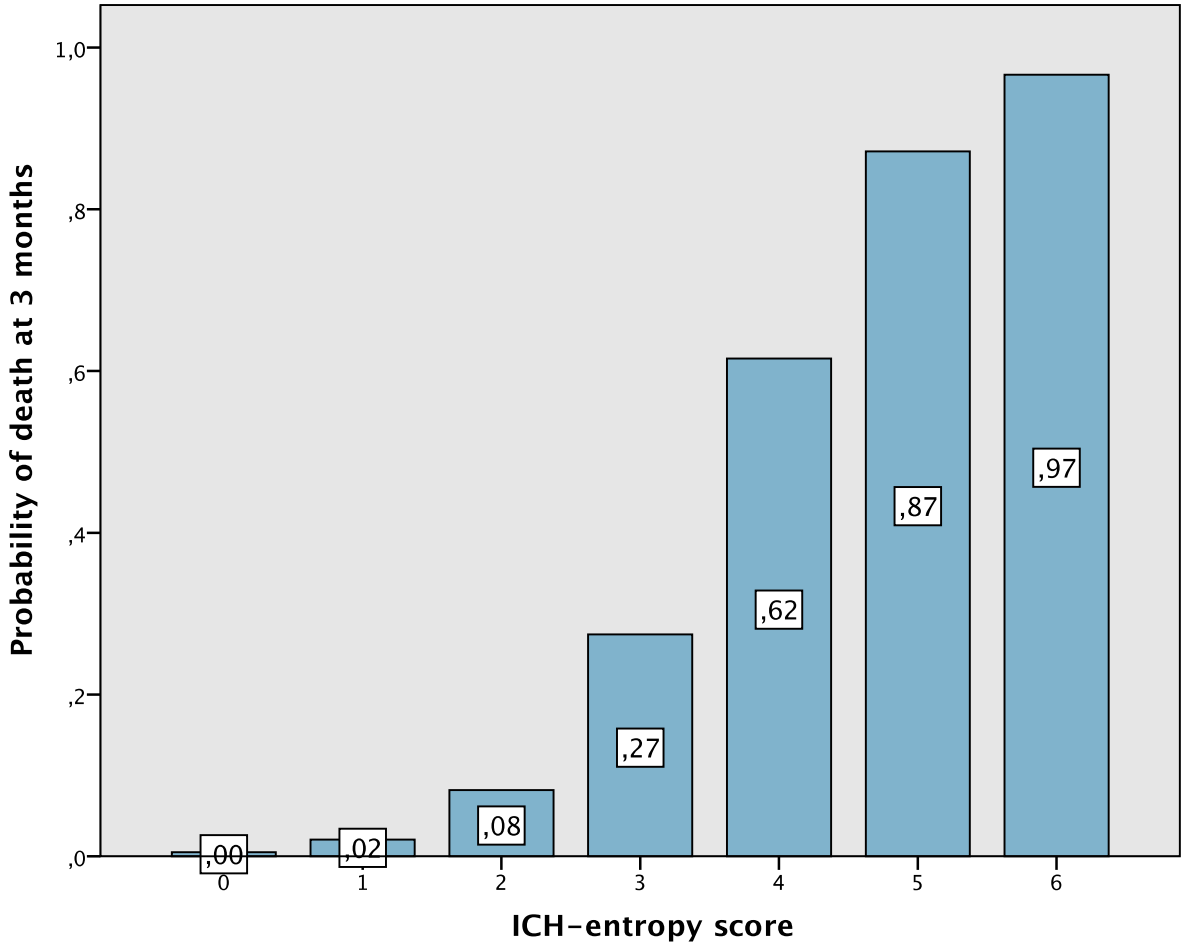

Figure 2. Probability of ICH-related death at 3 months by ICH entropy score.