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Transorbital Sonography for Early Prognostication of Hypoxic-Ischemic Encephalopathy After Cardiac Arrest

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ABSTRACT

BACKGROUND AND PURPOSE: **Early prognostication of the outcome in resuscitated post cardiac arrest (CA) patients remains challenging especially if treated with therapeutic hypothermia. Brain edema caused by hypoxic-ischemic encephalopathy (HIE) can indirectly be estimated by transorbital sonography (TOS) taking in account the optic nerve sheath diameter (ONSD). The prognostic value of this easy, safe, and reproducible technique was investigated in this study.**

METHODS: **A total of 49 patients, initially unconscious (Glasgow Coma Scale ≤6) after successful resuscitation, were enrolled into this prospective observational study. Sonographic ONSD measurements were performed twice on day of admission (day 0) and once on days 1 and 2 after CA. Beyond ONSD, established prognostic parameters like neuron specific enolase and gray-white matter ratios were assessed. Cerebral Performance Category (CPC) score served as outcome parameter.**

RESULTS: **A total of 15 (31.3%) patients had a good outcome (CPC-score 1–2), 8 patients (14.6%) had severe disability (CPC-score 3–4), and 26 (54.2%) had a fatal outcome (CPC-score 5). Already in the first measurement on day 0, nonsurvivors showed significantly higher ONSD values ($P < .001$). For predicting mortality, a threshold of 5.75 mm was calculated with a specificity of 100%. ONSD did not differ significantly depending on hypothermia ($P = .7009$).**

CONCLUSION: **Early and reliable prognostication of outcomes in patients with HIE can be simplified by ONSD values gathered with the use of TOS. Main advantages compared to other established markers are prognostication within the first 24 hours and independence from therapy with hypothermia. A higher level of accuracy can be reached by combining computed tomography (gray-to-white matter ratio values) and ONSD values.**

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Introduction

The early prognostication of the neurological outcome in resuscitated post cardiac arrest (CA) patients in the intensive care unit (ICU) remains challenging. For this purpose, clinical-neurological evaluation, laboratory biomarkers, functional electrophysiological as well as structural brain imaging examinations are used solely or in combination.[1,2]

Hypoxic-ischemic encephalopathy (HIE) can induce brain edema with an increase of the intracranial pressure, resulting to a reduced cerebral perfusion pressure that negatively influences the neurological outcome.[3]

Survivors of CA with suspected HIE usually undergo initial brain imaging using cranial computed tomography (CT). In this context, the gray-to-white matter ratio (GWR) serves as a structural prognostic marker, as the obliteration of gray and white matter decreases GWR values.[4] This procedure is recommended by respective guidelines (eg, American Heart Association Guideline 2015) with low false-positive ratios even in the early phase after the index event.[5] Nevertheless, the prognostic value of GWR remains controversial, since there is no consensus on a distinct GWR cutoff that may predict poor outcome and the sensitivity is comparatively low.[6] Additionally, it is unclear if hypothermia treatment alters the prognostic value of GWR.[4]

So far, absent or extensor motor response at ≥72 hours from arrest or early status myoclonus, bilateral absence of either pupillary and corneal reflexes or N20 wave of short-latency somatosensory evoked potentials, elevated values of neuron specific enolase (NSE) at 72 hours from arrest, as well as unreactive malignant electro encephalographic (EEG) patterns were identified as the useful but not fully robust predictors.[1] Restrictively, all of these predictors had been established in normothermic patients, while recent studies on outcome prognostication after CA have shown that hypothermia treatment alters these

prognostic parameters, for example, due to delayed clearance of sedative agents and opioids.[7] Meanwhile, patients with good neurological outcome have been described, despite extremely high NSE levels,[8] bilaterally absent evoked potentials,[9] as well as absent brain stem reflexes.[10] Furthermore, these parameters are predictive of outcomes only after 72 hours of post-CA.[1]

Consequently, even with a combination of negative prognostic parameters, no sufficient high level of certainty is reached in patients under hypothermia treatment, and currently it is difficult or even impossible to consider treatment termination in these patients. To optimally guide treatment decisions and strategies, a much earlier and more valid prediction of neurologic outcomes would be of high importance.

In the present study, we aimed to prospectively evaluate the prognostic value of the early assessment of the optic nerve sheath diameter (ONSD) in post-CA patients with suspected HIE. The ONSD is known to correlate with increased intracranial pressure.[11] The raised pressure in the cerebrospinal fluid inflates the dural sheath that surrounds the optic nerve.[12] The ONSD is easily measured sonographically by means of transorbital sonography (TOS), showing a high intra- and interrater reliability,[13] and it is known to be a good predictor of mortality in patients with severe traumatic brain injury.[11]

The ONSD can also be depicted by CT, where it has already shown to provide additional informative value on the prognostication on post-CA patients.[6] So far, the association between an early sonographic assessment of the ONSD and the outcome of resuscitated post-CA patients has been prospectively evaluated in only one recently published French study.[14] However, no threshold to clearly forecast in-hospital mortality could be described in this study, and the first ONSD measurement was performed 24 hours after CA. Therefore, in the present multicenter study we aimed to prospectively evaluate the prognostic value of sonographic assessment of ONSD in comatose patients after CA even on day of admission and in a larger study population.

Methods

During September 2015 and August 2017, a total of 50 patients were screened and 49 patients were enrolled into this prospective observational study in two German ICUs. All unconscious (Glasgow Coma Scale ≤ 6) patients ≥ 18 years old, admitted to ICU after successful resuscitation from CA, were screened. Exclusion criteria were as follows: unavailable ONSD measurement within 24 hours after CA (unavailable investigator, eg, due to patient admission during the weekend, early death, or major hemodynamic instability), CA of traumatic or neurological origin, previous cerebrovascular disease, facial trauma affecting the orbits and/or eyeballs, and previous history of ocular pathology such as exophthalmia or glaucoma. One patient had to be excluded according to the respective criteria with brain stem encephalitis as the putative reason for CA.

Resuscitation intervals were defined as no-flow duration (time from collapse to first cardiopulmonary resuscitation) and low-flow duration (time from first cardiopulmonary resuscitation to return of spontaneous circulation).

Biological parameters as NSE levels were measured on ICU admission or day 1 and 2, in most patients subsequently over the mentioned period. As a clinical parameter for patient outcome in the early phase, the Cerebral Performance Category (CPC) score was documented. As reported in the literature, a score of 1-2 was associated with a good outcome, 3-4 with severe disability and 5 with a lethal outcome.[1]

All patients were mainly treated by experienced cardiologists on the ICU aided by requested neurological consultations. Consequently, the treatment was not influenced by the study protocol and no exact time points for cerebral imaging and NSE analysis were defined.

This study was conducted according to the principles of the Declaration of Helsinki and approved by each of the two local institutional review boards (approval No. 2015-12 and No. 16–5770). All patients or their legal representatives gave their written informed consent.

Study Protocol

ONSD measurements were performed as previously reported.[15] In the majority of patients (28/49 patients = 57%) ONSD measurements were performed twice on day 0 and once on days 1 and 2 after CA. Measurements were performed by experienced investigators especially trained in TOS (center 1: CX50 Ultrasound System, Philips Healthcare, Amsterdam, the Netherlands. Two investigators, one of them accredited by the German Society of Ultrasonography; center 2: Aplio® XG Ultrasound System, Toshiba Medicals, Tochigi, Japan. Two investigators, both accredited by the German Society of Ultrasonography). All investigations were supervised by an accredited expert. Investigators were not involved in post-CA management. ONSD values were not communicated with the treating physicians to prevent any influence on the patients' outcomes (eg, preventing self-fulfilling prophecies).

Early brain CT scan was performed (both centers: Somatom Definition Flash, Siemens, Erlangen, Germany) at the discretion of the physician in charge and according to CA history. Cerebral edema was then assessed using the gray matter attenuation to white matter attenuation ratio (GWR) as previously described.[16] An independent investigator specialized in neuroradiology and blinded to clinical outcome secondarily evaluated the GWR.

Statistical Analysis

The primary end point of this study was survival, determined by CPC scale. Patients with CPC outcome scale 1–4 were classified as alive, respectively, death (CPC 5).

The mean of ONSD measurements, obtained from the left and right side was calculated and used for analysis. Continuous variables–ONSD, GWR, and NSE–-were described as median (interquartile range) or as mean ($\pm$ standard deviation). Results for categorical data were shown as n (%) and their relationship evaluated using χ^2 tests. t-Tests were determined for continuous variables. Values of $P < .05$ were considered significant. No adjustment for multiple testing was performed. Odds ratios were shown with the 95% confidence intervals. Spearman's correlation analysis was used to evaluate the relationship between continuous variables. Duration of hospitalization was compared using the nonparametric Wilcoxon rank-sum test. Survival time, measured from ROSC to death or discharge, was analyzed using Kaplan-Meier method.

The relationship between mortality and possible prognostic factors, ONSD, GWR, was modeled using a logistic regression.

Specificity derived from the logistic regression on survival was used to find the threshold of ONSD, which indicated a fatal prognosis without any false positive results.

Statistical analysis was performed with SAS Version 9.4.

Results

Patients' Characteristics

Forty-nine patients were investigated by four different physicians in two different centers. Most of them were examined in the Department of Neurology at the Clinic in Augsburg (Observer 1: $n = 31$ [63.2%]; Observer 2: $n = 9$ [18.4%]). Nine patients (18.4%) were included by the Department of Neurology, St. Josef-Hospital, University Clinic in Bochum.

Almost three-quarters of the patients were male (71.4%), which on average were 7 years younger (62.6 years) than the female patients (69.4 years). No significant differences were observed between survivors and nonsurvivors regarding gender, observers, as well as etiology of CA and resuscitation by laypersons (Table 1). Nonsurvivors were significantly older (10 years in average) than survivors ($P = .026$) and patients treated with hypothermia survived more often (77%, respectively, 46%, $P = .022$).

Fifteen (31.3%) patients had a good outcome (CPC score 1-2), 8 patients (14.6%) had severe disability (CPC score 3-4), and 26 (54.2%) had a fatal outcome (CPC- score 5).

Duration of hospitalization differed significantly between survivors and nonsurvivors with the first having been discharged after an average of 15.7 days and the latter deceased after a mean of 7.4 days ($P = .003$).

ONSD Measurements

ONSD values differed significantly between survivors and nonsurvivors at each time point (Table 2). The average time of measurements after ROSC is also given in Table 2. Due to organizational problems (eg, admission late at night or on the weekend), repeated ONSD measurements on day 0 were only available in 57% of the patients. The first measurement of ONSD in all subjects was done approximately 11 hours after resuscitation. At this first time point, the difference of ONSD values between survivors and nonsurvivors was .52 mm with significantly higher values in nonsurvivors ($P < .001$). ONSD values of survivors were stable over time, whereas nonsurvivors depicted an early and significant increase of ONSD (Figs 1 and 2). Three nonsurvivors were excluded from estimating potential prognostic factors because their death was not related to the CA.

With implementation of logistic regression analysis of the measurements within 24 hours after CA, a reliable association of predicted probabilities concerning both outcome groups could be identified with a percent concordant of 80.8%. For predicting mortality, a threshold of 5.75 mm of first ONSD measurement was derived from logistic regression model in a way that no cases were classified as false positive (100% specificity, positive predictive value 100%). Eight cases were classified as false negative at this threshold (60% sensitivity, negative likelihood ratio .4). To validate the threshold a survival analysis was performed for those patients with an ONSD value lower than 5.75 mm compared to those with an ONSD level above the threshold at the first measurement (Fig 3).

Influence of Hypothermia on Outcome and ONSD Measurements

Hypothermia therapy was an independent predictor for favorable outcome with 17 of 26 (65.4%) patients discharged alive in comparison to patients without hypothermic therapy with a survival rate of 31.6% (6 of 19 patients, $P = .022$). ONSD values did not differ significantly between patients treated with or without hypothermia (mean of first ONSD measurement [hypothermia] 5.62 mm compared to 5.68 mm [normothermia], $P = .7009$).

Comparison of Forecast Parameters

NSE values on day 0 did not differ significantly concerning survival but gained relevance on day 1 at the earliest (Table 2, Fig 4B).

The difference of GWR values in survivors and nonsurvivors was not statistically significant (Table 2, Fig 4A). Noteworthy is the fact that the first CT scan was performed always at the earliest after 24 hours, whereas the first ONSD measurement was performed after approximately 11 hours (Table 2). Therefore, a combination of the forecast parameters ONSD, GWR, and hypothermia did not provide the possibility of an earlier prognosis but significantly improved the reliability of the prediction by increasing the percent concordant to 92.2% (values of GWR/ONSD interpretation alone 58.9% and 85.6%, respectively).

Discussion

To the best of our knowledge, this is the second but largest multicenter study to prospectively assess ONSD by means of TOS as an early predictor of outcome in post-CA patients. The main finding of our study is that already with the first sonographic ONSD measurement within 12 hours after CA, we were able to predict fatal outcome with high specificity. For this purpose, a clear cutoff value of ONSD $\geq$5.75 mm could be determined.

At each time point of our examinations, a significantly larger ONSD was detectable in nonsurvivors compared to survivors. This significant enlargement of ONSD in our study is suggested to be caused by a malignant increased intracranial pressure due to cerebral edema caused by HIE. Recently, enlargement of ONSD as measured by CT has been reported to be a valid prognostic parameter for the outcome in patients after CA.[6] However, since the sonographic assessment of ONSD by means of TOS can easily be performed bedside on an ICU, TOS has great advantages over CT, like the abolition of time-consuming and sometimes risky transportation of ventilated patients to the radiological department, the possibility of frequent follow-up measurements in order to monitor the course of ONSD, etc.

The sonographic assessment of ONSD shows a high intra- and interobserver reliability.[13] The reproducibility and accuracy of sonographic measurement is even higher than the ONSD examination by magnetic resonance imaging (MRI).[17]

In the only prospective ultrasound study evaluating prognosis of post-CA patients so far, Chelly et al could also demonstrate in their smaller study ($n = 39$) that median ONSD values were significantly larger in nonsurvivors versus survivors.[14] However, although an ONSD value of $\geq$5.5 mm after adjustment of predictive factors was significantly associated with in-hospital

Table 1. General Characteristics of Patients at Baseline and on Admission According to Outcome

Variable	Overall $n = 49$	Survivors $n = 23$	Nonsurvivors $n = 26$	Fisher's Exact Test P
Male, sex, [n (%)]	35 (71)	17 (74)	18 (69)	.761
Age, years (mean [min-max])	65 [20-96]	59 [20-90]	69 [35-96]	.026
Observer [n (%)]				
1	31 (63)	14 (61)	17 (65)	
2	9 (18)	5 (22)	4 (15)	.072
3 and 4	9 (18)	4 (17)	5 (19)	
Etiology				
Ventricular fibrillation	29 (59)	17 (74)	12 (46)	
Asystole/pulseless electric activity	16 (33)	4 (17)	12 (46)	.09
Other	4 (8)	2 (9)	2 (8)	
Pretreatment by laymen [n (%)]	19 (40)	10 (45)	9 (35)	.175
Hypothermia [n (%)]	29 (60)	17 (77)	12 (46)	.022
Duration of hospitalization, days (mean [min-max])	11.3 [0-37]	15.7 [2-33]	7.4 [0-37]	Wilcoxon rank-sum test: .003

n = number of patients; min = minimum; max = maximum.

Table 2. Outcome and Prognostic Factors (Mean [± Standard deviation])

Variable	Overall $n = 49$	Survivors $n = 24$	Nonsurvivors $n = 25$	t-Test for Difference P
1. Measurement at admission day	$n = 49$	$n = 24$	$n = 25$	
ONSD	5.64 [± .50]	5.36 [± .43]	5.88 [± .44]	<.001
Time of measurement in hours	11.17 [± 6.46]	12.57 [± 5.32]	9.88 [± 7.21]	
2. Measurement at admission day	$n = 28$	$n = 14$	$n = 14$	
ONSD	5.71 [± .39]	5.54 [± .31]	5.88 [± .39]	.021
Time of measurement in hours	19.77 [± 5.40]	19.91 [± 5.40]	19.63 [± 5.60]	
3. Measurement at day 2	$n = 37$	$n = 19$	$n = 18$	
ONSD	5.78 [± .56]	5.56 [± .60]	6.01 [± .39]	.011
Time of measurement in hours	37.05 [± 8.67]	36.75 [± 5.81]	37.38 [± 11.24]	
4. Measurement at day 3	$n = 32$	$n = 18$	$n = 14$	
ONSD	5.79 [± .53]	5.63 [± .58]	6.00 [± .37]	.047
Time of measurement in hours	58.42 [± 9.43]	59.18 [± 6.41]	57.36 [± 12.73]	
NSE at admission day	$n = 15$	$n = 5$	$n = 10$	
	39.75 [± 23.61]	41.18 [± 18.84]	39.04 [± 26.60]	.88
NSE at day 1	$n = 24$	$n = 11$	$n = 13$	
	56.84 [± 52.07]	31.74 [± 13.31]	78.08 [± 63.11]	.022
NSE at day 2	$n = 17$	$n = 9$	$n = 8$	
	93.86 [± 107.83]	24.12 [± 10.12]	172.33 [± 114.77]	.008
GWR	$n = 30$	$n = 15$	$n = 15$	
	1.21 [± .10]	1.22 [± .08]	1.19 [± .11]	.45
Time of measurement in hours	28.70 [± 51.43]	25.88 [± 38.55]	31.95 [± 64.78]	

n = number of patients; ONSD = optic nerve sheath diameter; NSE = neuron specific enolase; GWR = gray-white matter attenuation ratio.

mortality, in contrast to our study they could not observe any threshold to discriminate a 100% in-hospital mortality rate. Beyond that, they describe higher median ONSD values in both groups (nonsurvivors = 6.7 mm; survivors = 6.5 mm) than in our study. This might be due to the fact, that Chelly et al performed the first ONSD measurement 24 hours after CA, and in our study this was already the case after approximately 11 hours. This highlights the importance of the time frame for the interpretation of ONSD values, especially concerning the prognostic significance: the discriminatory power of TOS was best within the first 12-24 hours, stressing the need for early investigation after CA. Furthermore, differences in the examination technique cannot be excluded. In our study ONSD evaluations in both centers were performed or at least supervised by instructors accredited by the German Society of Ultrasound (levels 2 and 3).

In another published TOS study, Ueda et al also described an association between ONSD enlargement and poor outcome.[18] In their single-center and only retrospective analysis of a total of 17 post-CA patients, mean ONSD was significantly larger in patients with an unfavorable outcome compared to those with a favorable outcome (6.1 ± .9 mm vs. 5.0 ± .9 mm, respectively). A normal ONSD value (defined as ≤5.4 mm) was an indicator of a favorable outcome (defined by a Glasgow Outcome Scale score of 4 or above), with a sensitivity of 83% and a specificity of 73%.[18] These results are consistent with our findings, however, Ueda et al measured ONSD only once and only in a time frame between 12 and 72 hours after CA.

Comparing the prognostic performance of sonographic ONSD estimation with the already established GWR on initial brain CT, a clear superiority of TOS could be determined in

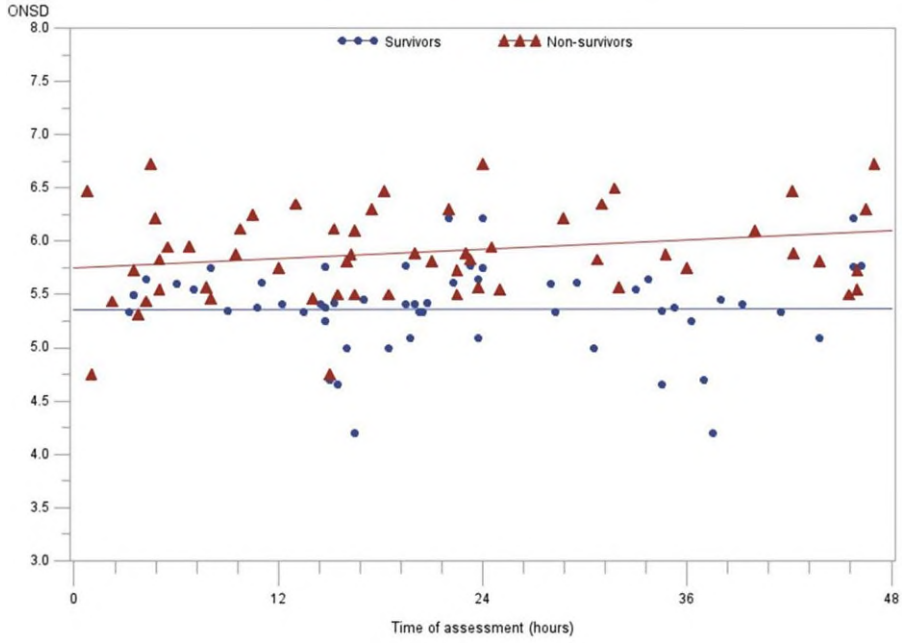

Fig 1. All measurements of optic nerve sheath diameter (ONSD) versus time of examination by outcome.

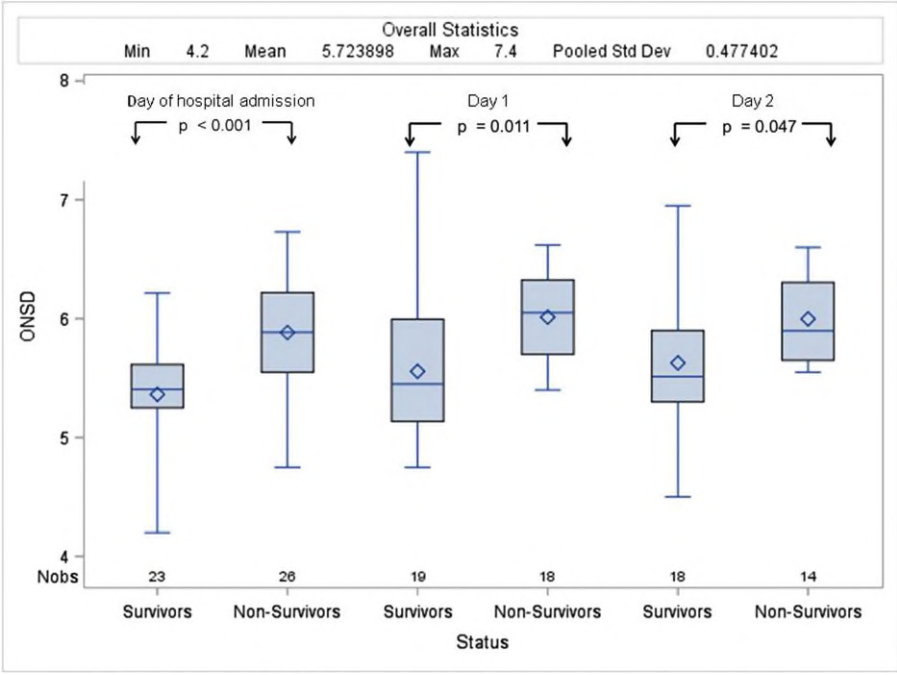

Fig 2. Box plot diagram comparing survivors and nonsurvivors depending on optic nerve sheath diameter (ONSD) values. min = minimum; max = maximum; Std Dev = standard deviation.

our study as a sound prediction of prognosis was feasible within the first 24 hours. These results were in line with the respective literature, as early prognostication within the first 24 hours using GWR values alone seems to be problematic especially in the context of hypothermic therapy.[19] The prognostic benefit of TOS is accompanied by many additional advantages of ultrasound, as it can be performed bedside rapidly even during therapeutic hypothermia. For CT examination, patients have to be transferred from the ICU to a CT room. This transport is associated with time and staff resources and sometimes also with medical risks for the patients.

Compared to the laboratory prognostic parameter of elevated serum levels of NSE, ONSD evaluation also showed the benefit of an earlier prognostication, as there was no significant difference in the NSE levels of survivors and nonsurvivors at day of admission. Another limitation of the NSE level as a predictor is that it has only been established in normothermic patients. Recent studies have shown that hypothermia

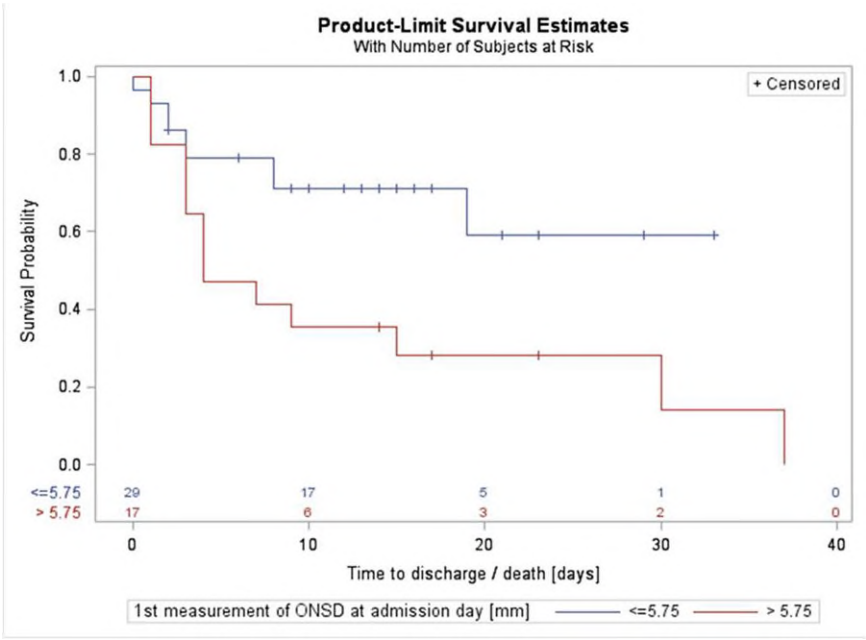

Fig 3. Survival estimates according to optic nerve sheath diameter (ONSD) values. A threshold of 5.75 mm was associated with a 100% specificity for outcome prognostication.

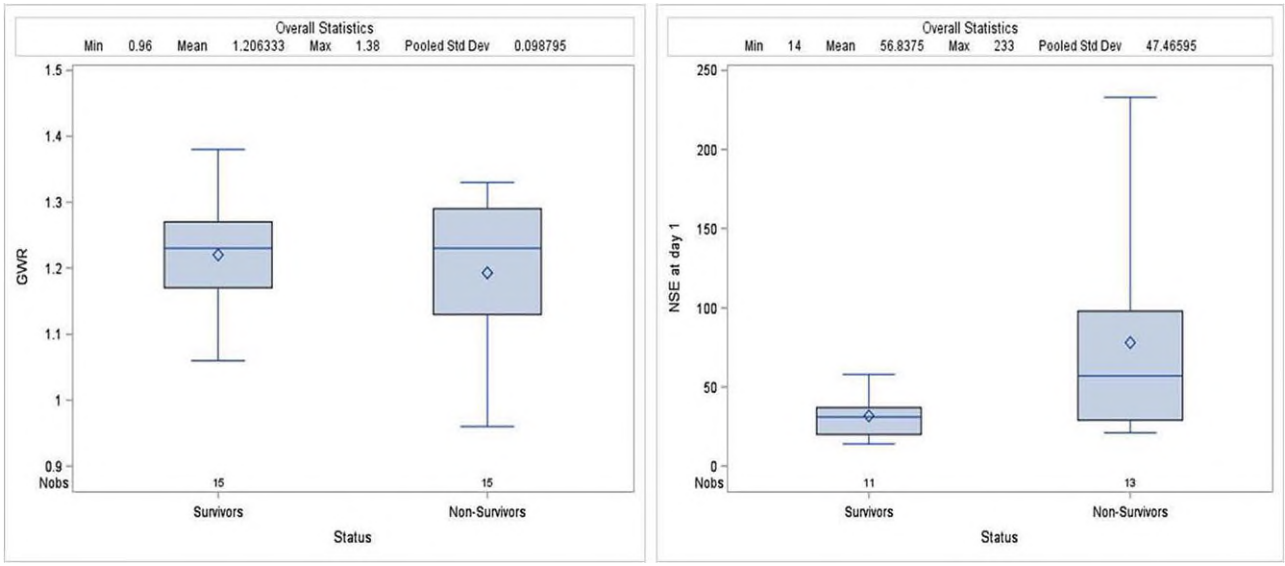

Fig 4. Box plot diagrams for comparison of gray-white matter attenuation rates (A) and neuron specific enolase (B) in survivors and nonsurvivors, respectively. min = minimum; max = maximum; Std Dev = standard deviation; NSE = neuron specific enolase; GWR = gray-white matter attenuation ratio.

treatment alters the prognostic value of this parameter, as patients with good neurological outcome have been described, despite extremely high NSE levels.[8] In the present study, the prognostic value of the estimated threshold of 5.75 mm on first ONSD measurement for predicting mortality was not altered by hypothermia treatment.

However, it should be mentioned as a limitation, that a precise comparison of the different prognostic parameters is not presented in our study. Since routine care and treatment was not influenced by the study protocol, the frequency as well as the time points of determination of the different parameters (NSE, GWR) was not matched and not standardized. Despite the relatively small number of patients in this study we were still able to define a clear-cut threshold value for prognostic discrimination.

In summary, early and reliable prognostication of outcomes in patients with HIE can be simplified by ONSD values measured using TOS. The main advantages compared to other established markers are prognosis within the first 24 hours and independence from therapy with hypothermia. A higher level of accuracy can be reached by combining GWR and ONSD values.

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