A Tree of Life? Multivariate logistic outcome-prediction in disorders of consciousness

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Inga Steppacher
University of Bielefeld

✉ Inga.Steppacher@Uni-Bielefeld.de*Corresponding Author*
ORCiD: https://orcid.org/0000-0001-5439-4840

Peter Fuchs
University of Bielefeld

Michael Kaps
Kliniken Schmieder Stiftung und Co. KG

Fridtjof Nussbeck
University of Bielefeld

Johanna Kissler
University of Bielefeld

Abstract

Background: Currently, the clinical outcome of patients with very severe head injuries and subsequent chronic disorders of consciousness is seen as generally very poor. Here, we specify individual outcome chances for disorders of consciousness (DOC) patients on the basis of clinical and EEG data and identify different subgroups of DOC patients, who vary substantially regarding their outcome chances.

Methods: We employed data from 102 patients with DOC and used standard clinical protocol data (age, etiology, diagnosis, gender) and early sensory (N100, Mismatch Negativity) and late cognitive (P300, N400) EEG event related potentials (ERPs) to predict patients recovery rates.

Results: Two significant prediction models emerged: In both, subgroups of patients with good (51%, tree 1) to very good recovery chances (97%, tree 2) could be identified. The first model was obtained from standard clinical data. The second model included late cognitive ERPs (N400 and P300) and resulted in considerably better patient classification. Moreover, when taking cognitive event related potentials into account, the standard protocol data did not add further significant information, neither did early ERPs (N100, MMN). This highlights that cognitive ERPs provide decisive information about an individual patient's prognosis.

Conclusion: The presented information about outcome chances of individual disorders of consciousness patients will be vital for these patients and critical for clinical professionals who have to direct specialized treatments and council relatives. Legal guardians and families, in turn, need to know what to expect in the future in order to prepare for the challenges ahead.

Keywords: Disorders of consciousness, Unresponsive wakefulness syndrome, Minimal consciousness state, Logistic outcome-prediction.

Background

Brain injuries are the number one causes of death and severe disability among the younger population in industrialized countries. Among the most severe disabilities resulting from brain injuries are disorders of consciousness (DOC), encompassing the clinical syndromes of the unresponsive wakefulness syndrome (UWS [1]; (former vegetative state [2, 3]) and the minimal conscious state

(MCS [4]). In the former, patients show no signs of self-awareness or awareness of their surroundings [2]. In the latter, patients show some limited, often inconsistent signs of awareness which can reach from sole eye-fixation to the following of simple commands. A patient is considered to have improved above MCS if functional communication and/or functional object use has been re-established [4]. Both syndromes can be steps towards recovery but can also become permanent conditions in which the patient can survive for many years without any change of cognitive status. Thus, a reliable identification of prognostic factors is of importance to all, the patients themselves, family members, as well as for the medical staff involved.

On the group level, variables such as age, diagnosis, and etiology have been repeatedly found to be statistically reliable prognostic indicators of outcome [3, 5, 6]. Here, younger age, a traumatic injury and a quick transition into the state of MCS are predictors of a favorable outcome (recovery of communicative abilities), whereas an age of over 45 or 50 years, prolonged UWS and an anoxic event are considered to be predictors of an unfavorable outcome (no recovery until death).

Various cerebral measures of information processing have also been found to correlate with outcome (see for example: [7, 8]). These include several, mostly auditory, electroencephalographic event related potentials (ERPs). For example, the absence of the N100, an index of cortical sensory stimulus registration, is considered to be predictive of a negative outcome [9]. The presence of the so-called mismatch negativity (MMN), indicating an automatic detection of deviant stimuli in continuous auditory stimulation streams, on the other hand, has been shown to be a positive sign [10, 11]. The presence of a P300, reflecting higher-order stimulus discrimination, also often correlates with a positive outcome [11, 12]. Another recently discussed and possibly very promising ERP is the N400, the cortical reaction to semantic violations in spoken speech. Although rarely found in patients, its presence correlates highly with a positive outcome [13].

However, although all these separate prognostic factors are important and relevant, they hold limited information for clinical daily routine. This is mainly because the typical patient presents with a highly individual set and combination of positive and negative predictors, which can interact in various ways. For instance, a young patient with an anoxic event may demonstrate ERPs like the N100 but no

detectable MMN. In this case, the young age and the N100 are positive predictors whereas the anoxic cause, as well as the missing MMN would foretell a negative outcome. From extant scientific studies, it remains unclear how these prognostic factors interact and how physicians are supposed to weigh factors when a patient presents both, positive and negative predictive factors at the same time. Currently, physicians may overestimate the probability of extremely unfavorable outcomes after severe brain damage [14, 15]. This is especially concerning, since physicians are often asked to provide counseling regarding end of life decisions. Self-fulfilling prophecy can result, if clinicians rate survival chances (or a good outcome) as very poor, advise discontinuation of life sustaining measures, patients die because life-sustaining measurements are ended, and clinicians are confirmed in their prognosis. In fact, as a Canadian retrospective study shows, it seems that up to 70% of deaths in patients with severe TBI on intensive care units result from termination of life-sustaining measures [15]. So, there is little quantitative information available about the natural disease course and, for DOC in particular, the likely outcome of various sub-groups of patients.

For the acute phase of TBI-induced coma, some attempts have been made to provide physicians with 'multi factor models'. For example, based on data from 102 patients, Jain at al. [16] employed the presence / absence of pupil responses, need of ventilation and Glasgow Coma Scale (GCS) improvement within the first 24h after the incident in a prediction-tree, identifying a subgroup of patients (with pupil responses, no need of ventilation and an increase in GCS scores within the first 24h), where survival rate increased from 6.1% to 57.1%. The prediction tree of Rovlias and Kotsou [17] tested a total of 16 known predictive factors on outcome data of 345 acute patients. The best predictive tree resulted from 8 factors (GCS, age, pupillary responses, computer tomographic (CT) findings, hyperglycemia and leukocytosis) with a predictive accuracy of 86.84%. Furthermore, from the 'International Mission for Prognosis and Analysis of Clinical Trials in TBI' (IMPACT; [18]) with over 9000 patients, prognosis chances can be calculated with three models of increasing complexity, yielding the 6 month outcome of adult patients with moderate to severe head injury. Sadly, IMPACT treats death, UWS and severe disability indiscriminately as unfavorable outcome. Although all current models provide physicians with helpful data about likelihood of a favorable or unfavorable outcome in

the acute phase, given the data of the same DOC patient, the different models result in very different forecasted recovery chances [19].

Moreover, to the best of our knowledge, no prediction model exists for the post-acute phase when patients have already entered into the stages of severe disorders of consciousness (DOC). This might be due to the fact, that in order to calculate a prediction tree with various branches, a large number of patients is needed. Such numbers are hard to obtain for DOC patients since, although growing in numbers, DOC is still a rare and sometimes slowly changing syndrome, requiring long follow-up intervals. Moreover, clinical routines and documentation are rarely standardized between centers, and sometimes the whereabouts of post-acute brain damaged patients are not even known.

The aim of the present study is to develop prediction models for DOC outcome on the basis of data from 102 DOC patients, testing the predictive value of clinical prognostic factors as well as ERPs regarding DOC patient outcome after eight years on average (range 2 to 17 years). The models demonstrate the influence of presence or absence of various factors on the probability of a favorable (regaining communicational skills) or unfavorable (permanent UWS or MCS until death) outcome. We calculated predictions for two possible scenarios: in the first scenario patient demographics were taken into account, which can be easily obtained for every patient (diagnosis, age, etiology, gender). In the second model, we tested outcome prediction relying on information on ERP statuses (N100, MMN, P300 and N400).

Methods

The initial sample consisted of 175 patients with UWS (n=92) or MCS (n= 83). Outcome data could be obtained from 102 patients (43 MCS patients, 59 UWS patients) who were included in this study. The outcome follow-up was a structured telephone interview 2 to 15 years after the patients' discharge. Here, in most cases, relatives of the patients were asked about the physical and cognitive abilities of the patient. Because of very high misdiagnosis rates even with trained clinical staff, relatives were not asked to distinguish between UWS and MCS patients. We therefore asked relatives, whether or not patients were able to functionally communicate (via speech, eye-blink code or any other means), expecting that this hallmark could be reported reliably. According to this, we regarded patients as

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'recovered' if functional recovery was obtained and considered a patient as' not recovered' if he or she was still UWS or MCS.

Patients were initially treated at the Neurorehabilitation Hospital 'Kliniken Schmieder' (Allensbach, Germany) between 1994 and 2005. From these patients, clinical files were available and all had undergone ERP examination, including N100, MMN, P300 and N400 ERPs (for paradigm description, ERP analysis, ERP scoring and illustration of individual responses see supplement 1). All ERPs were obtained during the first weeks of rehabilitation. The patients' cognitive functioning was, for one, evaluated using the coma remission scale (CRS). The CRS was developed in Germany [20] specifically to monitor and protocol the improvements of coma, UWS and MCS patients in early rehabilitation units and was used in all patients as part of the clinic routine. We further analysed daily clinical protocols from nurses and therapists for any signs of (even suspected) conscious behaviours (like eye-following or eye-fixation). Patients were assigned to be in UWS if there was no indication of conscious behaviour up to the time of ERP-testing. If there was any indication of conscious behaviour, patients were assigned to be in MCS.

Detailed descriptions of the patients within the sample can be obtained from supplemental data of previously published articles [13, 21] where we have reported on the prognosis value of P300 and N400 as single predictors. N100 and MMN were not included in the previous reports.

Statistical Analysis

The analyses were conducted using SPSS 21 (IBM SPSS Statistics for Windows, Version 21.0) and R [22]. Several logistic regression models were performed to assess the impact of the prognosis factors on the likelihood that patients would recover communicative abilities. Model 1 included age, diagnosis, etiology and gender as variables. Model 2 additionally included early sensory (N100, Mismatch Negativity) and late cognitive (P300, N400) ERPs. Model variables were binary-coded as follows: Diagnosis: minimal conscious state (MCS) = 0, unresponsive wakefulness syndrome (UWS) = 1; female = 0, male = 1; event related potentials: Yes present = 1, No, not present = 0. Etiology was divided into: traumatic brain injury, hypoxic-ischemic injury (as well as respiratory arrest) and others (like Meningitis, anesthesia accident, lightning stroke, epileptic seizure, etc.). Age was divided into

younger than 31.5 years, between 31.5 years and 58.5 years and above 58.5 years. This categories were effect coded with Yes= 1 and No= 0.

The resulting models (Model 1 and 2c) are shown in Table 2; a graphical presentation is given in Fig. 1 and 2. In the second model an upwards strategy was used. Factors were only included if the model comparison was significant regarding the likelihood-ratio-test (α=.05). Only Diagnosis, P300 and N400 increased the model fit significantly, although N100 and MMN were also tested. The first and the second model are not nested, and thus models cannot be compared via likelihood ratio test.

Therefore, the Akaike Information Criterion (AIC; [23]) was computed for comparing the models.

Results

Demographic variables of the patients can be seen in table 1.

Two prediction models of 102 severely head injured patients in a DOC are presented in Fig. 1 and 2. For sake of clarity of presentation we present the model results comparable to those of a partitioning tree although all model parameters are simultaneously estimated in logistic regressions. The base-rate for re-establishing some form of communication is .33. Testing demographic information in the first model (see Fig. 1, Table 2, Model 1) revealed that the best predicted probability for a favorable outcome results for young female MCS patients with TBI or Other causes (43% and 51% respectively).

In the second model, information about presence or absence of ERPs were analyzed (Fig. 2, Table 2, Models 2a-c). Here a very good chance of recovery is prognosticated for MCS patients with both N400 and P300 (up to 97% recovery chance). However, there is also a subgroup of UWS patients, namely those with both ERPs present, that reaches very good outcome predictions of up to 92%

Discussion

Using logistic regression models, this study examined whether it is possible to identify from a fairly large sample of DOC patients, sub-samples with favorable outcome probabilities.

Our most important finding is, that it is indeed possible to identify subgroups of patients with much better chances for a good outcome (regaining the ability to communicate) than currently suggested by most physicians.

This is highly important since in clinical practice DOC patients are often considered to be a homogeneous group of hopeless patients, representing the collateral damage of modern medicine [24, 25]. This may lead into a vicious circle of forecasted devastating outcome, discontinued life support, occurring death and the subsequent reinforcement of the devastating prognosis [14]. Our data show that DOC patients are not as homogenous as they may seem and vary greatly in their outcome chances. From our results, it is possible to identify patients with a good prognosis by combinations of known and easily obtainable factors like diagnosis, age, etiology and gender. Furthermore, ERPs can help to further differentiate patients within the same diagnosis category. Patients with both, a N400 and a P300 had the best chances of a favorable outcome (97%) with the presence of a N400 causing the biggest change in predicted probabilities. Thus, electrophysiological indicators of high-level cognitive processing are important outcome predictors, whereas lower-level sensory and perceptual processing added no further information to our outcome classification. Moreover, when full electrophysiology measures are available, only diagnosis played an additional significant role. Furthermore, the AIC of our second model is with 74.66 considerably smaller than the AIC from the first model (100.51), indicating that model 2 indeed predicts outcome better [23]. This further highlights the need for using standardized electrophysiological measures for DOC patients in order to give the most exact prognosis available before making irreversible recommendations.

In both regression models, the current state of a patient emerges as the first powerful predictor of outcome. The patients in this study were either assigned to the UWS or MCS group based on careful medical file review. Medical files included daily therapeutic reports, medical bedside diagnostics and daily care protocols from the rehabilitation facility as well as discharge reports from previous acute clinics. Patients were assigned to the UWS group when there was no mention of possible awareness in any protocol up to the ERP testing of the patient. Since our diagnosis takes into account weeks of close observation of the patients, we assume that we are not likely to have misdiagnosed as many patients as are reported by the literature, which would be up to 40% of the UWS patients [26–28]. Our results clearly highlight the need of accurate diagnosis which is worth an additional effort since the knowledge about the correct diagnosis and the changes in outcome chances are very important for

physicians, families, facilities and, in particular, the patients, since the correct diagnosis could make a huge difference for actually aware patients who are mistaken for being unaware.

The first model, using patient demographics, is significantly better in classifying patient outcome (overall correct classification / OCC: 72%) than the standard assumption that no recovery will occur (which is correct in 67% of cases in our data). Here, in general, known results can be replicated with younger patients having better chances than older ones [3, 5]; MCS has better recovery chances than UWS [6]; female patients have slightly better general recovery chances than male patients [29], and hypoxic causes are associated with the lowest recovery chances [5, 6]. In our study, recovery chances vary between 6% for an older male patient in UWS with a hypoxic cause and 51% for a younger female patient in MCS with a cause from the category 'others' but also with TBI (around 45%).

In the second model, after the diagnosis, the pre- or absence of a N400 and the pre- or absence of a P300 cause significant changes in outcome prediction. In this model, the highest predicted chance of recovery with 97% is reached for a MCS patient with both, detectable N400 and P300. The lowest predicted recovery chance (around 10%) unfolds for UWS patients with neither a N400 nor a P300. This model reaches a total of 80% of correct classifications. This makes the second model more informative than the first. It comes close to the correct classification level of Rovlias' and Kotsou's model for acute patients with traumatic brain injuries (TBI), which reaches 86.84%. However, the Rovlias and Kotsou model actually needs eight factors to reach this result [17].

One limitation of our regression-models is, that we started with 'only' 102 patients, although this is a fairly large number for this field and actually the very same as in the model of Jain et al. [16]. Additionally, according to Peduzzi et al. [30], consistency of logistic regression estimates depends on the number of events per variable, sample size, and the number of predictors. Peduzzi's simulated data suggests, that in our case the maximum number of predictors given the sample size would be three or four. Therefore, a model calculated from a bigger patient group to begin with could very well result in a more fine-grained model, taking more factors into account and reaching even more overall correct predictions. In such a model, factors that at present did not contribute significant information such as early ERPs, could turn out to be of added value. Those numbers, however, would be very hard

to obtain since most facilities loose contact to patients after discharge, which makes them and their long-term outcome difficult to acquire. But long-term follow-ups are needed to correctly classify recovered and not recovered patients since UWS and MCS can be very slow changing syndromes [19, 20, 31]. In our sample of 102 patients, six patients recovered consciousness and communicative skills only after three to five years in UWS (5 patients) or MCS (1 patient). In shorter follow-up periods, the potential of these patients would have been missed.

Clearly, our results call for validation in additional samples. Unfortunately, we are not able to run a cross-validation within our sample due to sample size requirements. Nevertheless, we used the rpart-package [32] (method = "class") to investigate if our results remain stable across different analytic strategies, namely recursive partitioning. Recursive partitioning strives to correctly classify members of the population by splitting it into sub-populations. Within this process, the first variable is identified which best splits the data into two groups. After that, the next variable is tested independently for each sub-group. The resulting models can therefore be presented as binary trees. Using all predictors simultaneously, we found that again the occurrence of a N400, and for those with a N400, age and the occurrence of a P300 could be identified as important nodes producing the best recovery rates (Fig.3).

Conclusion

In sum, in the present study, which is to our knowledge the first of its kind, it was possible to identify subgroups of DOC patients with astonishingly high chances of good recovery, which was defined here as, at least, regaining communication skills. Our study further highlights the usefulness of higher cognitive event related potential measures, like the P300 and the N400. We argue for the need of making these measures a standard examination for DOC patients since they hold more prognostic information than the standard clinical data. All obtainable information should be used before physicians council families about prolonging or terminating a patient's life support.

Abbreviations

UWS - Unresponsive wakefulness syndrom

MCS - Minimal conscious state

DOC - Disorders of consciousness

TBI - Traumatic brain injury

ERP - Event related potential

MMN - Mismatch negativity

GCS - Glasgow coma scale

CRS - Coma remission scale

IMPACT - 'International Mission for Prognosis and Analysis of Clinical Trials in TBI'

CT - Computer Tomography

Declarations

Ethics approval and consent to participate

The study is an analysis of already anonymized data which were originally obtained at the Schmieder

Kliniken, Allensbach. Therefore, neither consent of participants nor ethical approval is applicable (EU-

Datenschutzgrundverordnung 2018, EU-DSGVO)

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding

author on reasonable request.

Competing interest

The authors declare that they have no competing interests

Authors' contributions

IS: Concept and design, preparing the data, drafting the manuscript

PF: statistical analysis of the data, revision of manuscript, final approval of manuscript, accountable

for all aspects.

MK: acquisition of data, preparing of the data, revision of the manuscript, final approval of

manuscript, accountable for all aspects.

FN: statistical analysis of the data, revision of manuscript, final approval of manuscript, accountable

for all aspects.

JK: conception and design of the study, revision of manuscript, final approval of manuscript,

accountable for all aspects.

All authors read and approved the final manuscript

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Tables

Table 1: Demographics for the DOC patients

	MCS patients n= 43	UWS patients n= 59	Total n= 102
Mean age at event (Range)	45 years (17 – 72 years)	44 years (17 - 75 years)	45 years (17 - 75 years)
male / female (%)	28 (65%) / 15 (35%)	48 (81 %) / 11 (19%)	76 (74.5%) / 26 (25
TBI/ anoxia /others (%)	24 (56%) / 6 (14 %) / 13 (30 %)	25 (43%) / 19 (32 %) / 15 (25 %)	49 (48%) / 25 (24. / 28 (27.5%)
Time until follow up in years (SD) (Range)	8.02 (3.54) (2-17 years)	8.8 (3.14) (4-15 years)	8.49 (3.31) (2-17 years)
Most common cause of death	Pneumonia	Pneumonia	

Table 2. Logistic Regression Analyses

	Estimates					Model Results				
	B	SE	Z	P	Exp(B)	OCC		Df	p	AIC
Baseline						.69				102.1
Intercept	-0.81	0.24	-3.35	.001	.45					
Model 1						.72	.12	11.61	5	.041	100.5
Intercept	1.48	1.04	1.42	.155	4.40					

Predictor	B	SE	z	p	Exp(B)	OCC	McFadden's R²	χ²	df	p	AIC
Age	-0.04	0.02	-1.90	.058	0.96						
Diagnosis	-1.24	0.54	-2.30	.021	0.29						
Etiol. (TBI)	0.02	0.38	0.06	.949	1.02						
Etiol. (HYP)	-0.37	0.44	-0.84	.399	0.69						
Etiol. (other)	0.35	0.41	0.84	.399	1.42						
Gender	-0.23	0.57	-0.40	.688	0.80						
Model 2a						.69	.06	6.38	1	.012	98.74
Intercept	-0.17	0.34	-0.51	.613	0.84						
Diagnosis	-1.24	0.50	-2.47	.014	0.29						
Model 2b						.81	.28	21.45	1	<.001	78.29
Intercept	-0.76	0.40	-1.89	.058	0.47						
Diagnosis	-1.33	0.61	-2.19	.029	0.26						
N400	3.28	0.86	3.81	<.001	26.51						
Model 2c						.80	.33	5.64	1	.018	74.66
Intercept	-1.37	0.52	-2.64	.008	0.25						
Diagnosis	-1.22	0.63	-1.92	.054	0.30						
N400	3.52	0.91	3.85	<.001	33.89						
P300	1.53	0.65	2.34	.019	4.61						

Notes. OCC: Overall correctly classified cases expressed as relative frequency when cut-off probability

of $p< .05$ is used; McFadden's R² = chi square statistic for model comparison; AIC: Akaike information

criterion (lower values indicate better model fit);

Etiol.: Etiology, TBI: traumatic brain injury, HYP: hypoxic-ischemic injury as well as respiratory arrest,

Others: Meningitis, anesthesia accident, lightning stroke, epileptic seizure
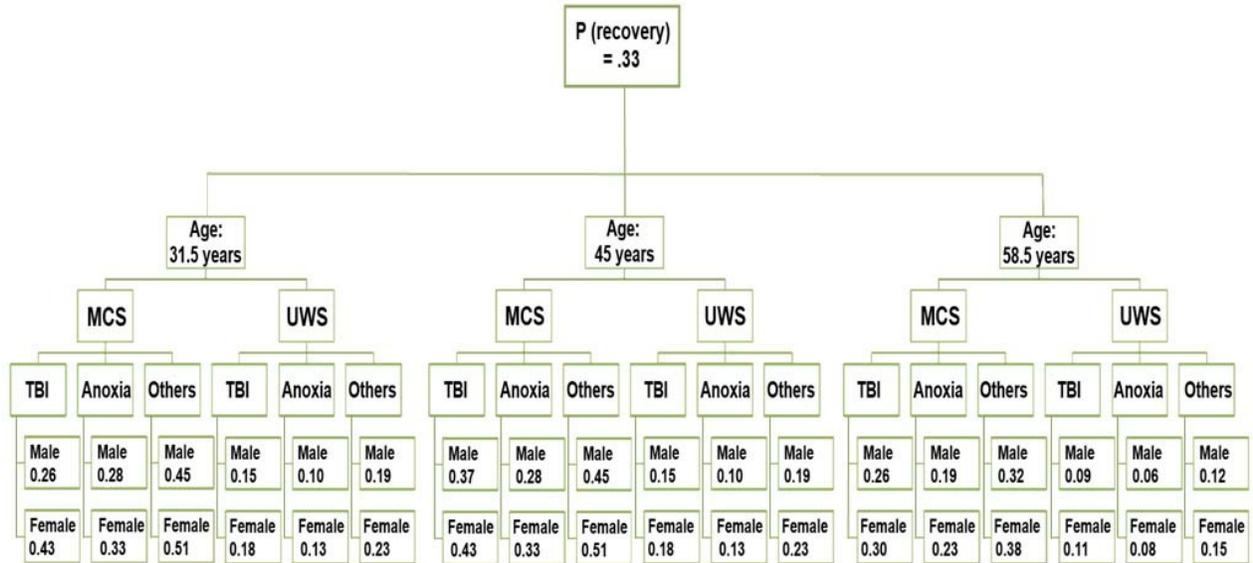
Figures

Figure 1

Regression model based on clinical and demographic data from 102 patients with disorders of consciousness (DOC). The numbers in the lower squares represent the predicted probability of a favorable outcome (recovery of communication skills). The predicted probability of a favorable outcome without any knowledge about a patient was 33% in our patient sample.
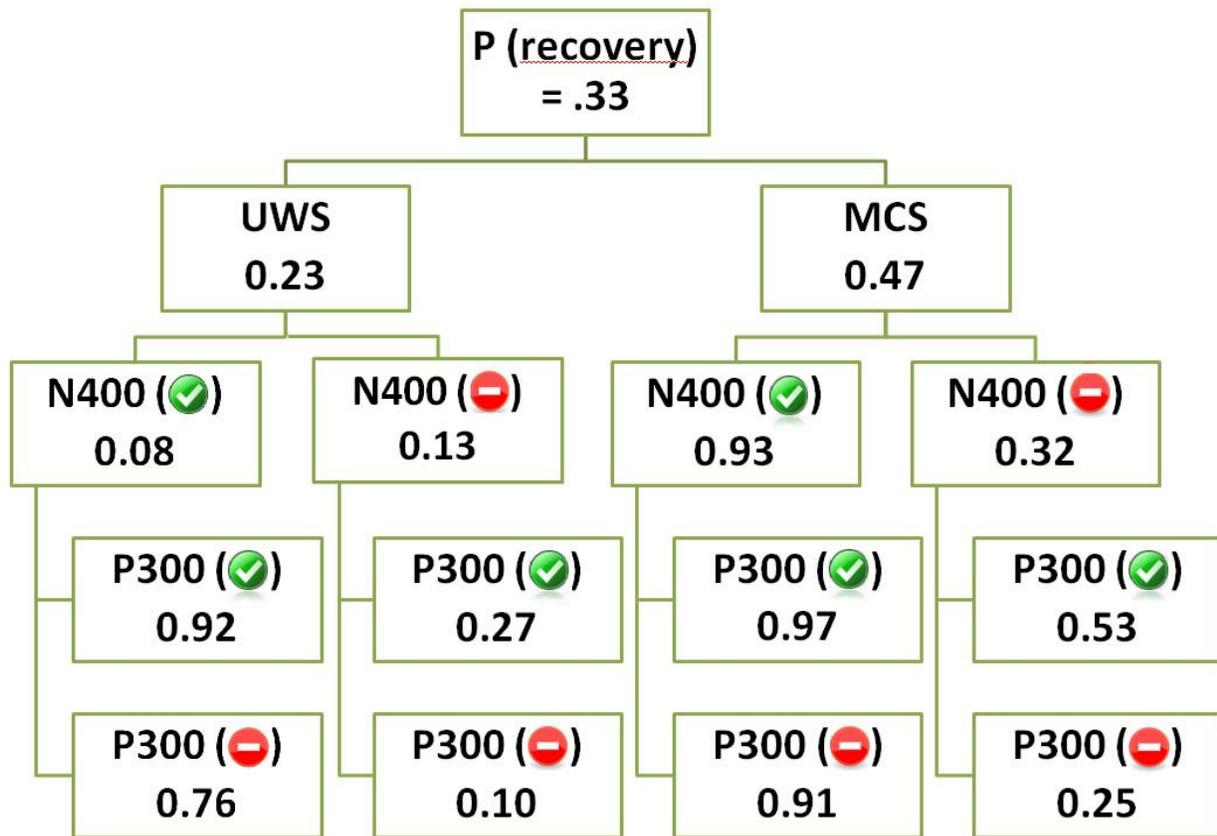
Figure 2

Regression model based on ERP data from 102 patients with disorders of consciousness (DOC). The numbers in the squares represent the predicted probability of a favorable outcome (recovery of consciousness and communication). Chi-square calculation (see table 2) demonstrates that every factor in the tree contributes significantly.
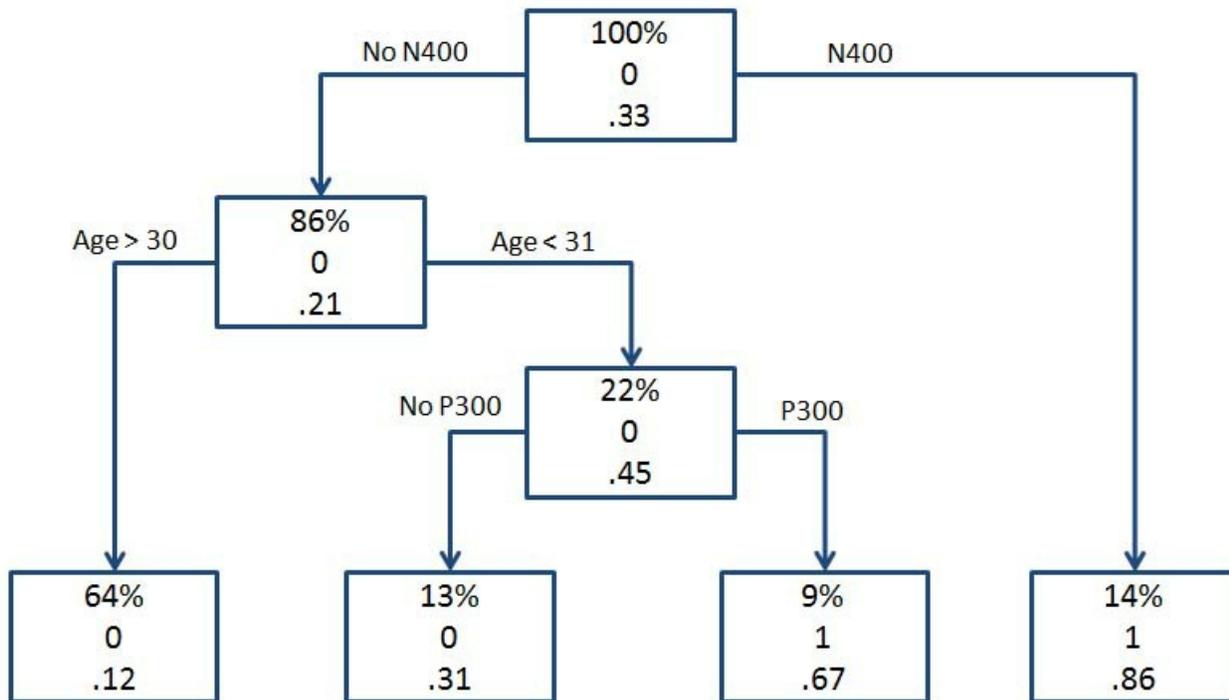
Figure 3

Graphical presentation of the recursive partitioning. The boxes represent the nodes of the tree. The first number (%) indicates the percentage of the sample at this node. 0 (no recovery) or 1 (recovery) present the most likely state of the participants. The last number presents the likelihood for being recovered at this node. The annotations at the arrows present the predictor at the preceding node. The last box with entries (14%; 1; .86), for example, indicates that 14% of the participants had a N400 reaction, they were mostly recovered (1) with a likelihood of .86. Patients being younger than 31 years without N400 reaction but with P300 have a probability of recovery of .67. This group consists of 9% of the sample.

Supplementary Files

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