

Systematic review of early prediction of poor outcome in anoxic-ischaemic coma

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Summary

Background Studies to assess the prognostic value of early neurological and neurophysiological findings in patients with anoxic-ischaemic coma have not led to precise, generally accepted, prognostic rules. We did a systematic review of the relevant literature to assess whether such rules could be derived from the combined results of these studies.

Methods From Medline and Embase databases we selected studies concerning patients older than 10 years with anoxic-ischaemic coma in which findings from early neurological examination, electroencephalogram (EEG), or somatosensory evoked potentials (SSEP) were related to poor outcome—defined as death or survival in a vegetative state. We selected variables with a specificity of 100% for poor outcome in all studies, and expressed the overall prognostic accuracy of these variables as pooled positive-likelihood ratios and as 95% CIs of the pooled false-positive test rates.

Findings In 33 studies, 14 prognostic variables were studied, three of which had a specificity of 100%: absence of pupillary light reflexes on day 3 (pooled positive-likelihood ratio 10.5 [95% CI 2.1–52.4]; 95% CI pooled false-positive test rate 0–11.9%); absent motor response to pain on day 3 (16.8 [3.4–84.1]; 0–6.7%); and bilateral absence of early cortical SSEP within the first week (12.0 [5.3–27.6]; 0–2.0%). EEG recordings with an isoelectric or burst-suppression pattern had a specificity of 100% in five of six relevant studies (pooled positive-likelihood ratio 9.0 [2.5–33.1]; 95%CI pooled false-positive test rate 0.2–5.9%). These characteristics were present in 19%, 31%, 33%, and 33% of pooled patient populations, respectively. For the 11 SSEP studies, results did not significantly differ between studies in which the treating physicians were or were not masked from the test result, prospective and retrospective studies, studies with short and long follow-up periods, and studies with high or low overall poor outcome.

Interpretation SSEP has the smallest CI of its pooled positive-likelihood ratio and its pooled false-positive test rate. Because evoked potentials are also the least susceptible to metabolic changes and drugs, recording of SSEP is the most useful method to predict poor outcome.

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Introduction

Persistent coma after global cerebral ischaemia is a serious clinical disorder. The prospect of neurological recovery is poor for many patients, and clinicians are often confronted with the question of whether continuation of treatment is worthwhile. To answer this question, it is important to know which clinical features determine prognosis.

The many prognostic studies in patients with anoxic-ischaemic coma have so far not produced results on which a uniform policy can be based.¹ Reasons for this are: the small numbers of patients in separate studies, resulting in statistical uncertainty, and the use of different sets of variables in different studies, leading to incomparable results. We therefore did a systematic review of the relevant clinical and neurophysiological literature to find out whether accurate prognostic rules could be derived from the combined results of these studies.

Methods

Literature search

We collected studies available from the biomedical literature in which early neurological or neurophysiological features of patients with anoxic-ischaemic coma were related to outcome by doing a search in Medline (from 1966) and EMBASE (from 1982) for such reports in English, German, and French. The keywords used were: anoxia (cerebral), ischaemia (cerebral), heart arrest, hypotension, shock, postoperative complications, respiratory insufficiency, resuscitation, or drowning, combined with coma or Glasgow Coma Scale. The reference lists of the relevant articles were scanned for additional studies.

Study selection

Studies were selected according to the following criteria: inclusion of patients with anoxic-ischaemic coma only, or, when mixed populations were studied, presentation of separate data from patients with anoxic-ischaemic coma. We did not distinguish between different causes of ischaemic coma, but excluded studies and patients with coma from other medical conditions or trauma. Our analysis was primarily aimed at adult patients, so we excluded young children and new-born babies. Other criteria for study selection were: a lower age limit of 10 years; reporting of unselected, consecutive cases; unequivocal description, classification, and timing of recording of clinical and neurophysiological features; presentation of data about single clinical or neurophysiological features related to outcome; presentation of outcome data in such a way that data for the combined outcome of death or vegetative state versus other outcome states could be extracted. This last criterion was chosen because death and vegetative state are generally accepted as poor outcome, whereas classification of poor outcome can be disputed for any other outcome state.

Data extraction

From the selected reports the following data, generally considered important for the prediction of neurological outcome, were extracted: Glasgow Coma Score (GCS, and/or its separate compounds); pupillary light reflex (present/absent); corneal reflexes (present/absent); eye movements (present/absent); epilepsy or myoclonus (present/absent); epileptic and/or myoclonus status (present/absent); somatosensory evoked potentials (SSEP) from median nerve stimulation (present: cortical responses [N20, the earliest cortical response after median

| Factor | Study reference | Number of patients studied | Prevalence poor outcome (95% CI) | Prevalence poor test (95% CI) | Sensitivity range | Specificity range |
|---|---|----------------------------|----------------------------------|-------------------------------|-------------------|-------------------|
| Pupillary reactions | | | | | | |
| Absent on admittance | 12, 19, 21, 22 | 491 | 59% (55-63) | 22% (19-26) | 30-50% | 69-100% |
| Absent on day 3 | 12, 18, 19 | 152 | 68% (61-76) | 19% (13-25) | 22-55% | 100% |
| Motor response | | | | | | |
| M1-3 on GCS in first 24 h | 11, 24, 31, 38 | 269 | 58% (53-64) | 73% (68-79) | 63-95% | 30-79% |
| M1-3 on GCS day 1 | 11, 17 | 87 | 69% (58-78) | 76% (67-85) | 85-87% | 42-59% |
| M1-3 on GCS day 3 | 15, 21, 24 | 307 | 73% (66-79) | 64% (57-71) | 70-100% | 29-100% |
| M1-2 on GCS day 3 | 12, 15, 18 | 171 | 70% (63-77) | 48% (41-55) | 56-92% | 93-100% |
| M=1 on GCS day 3 | 12, 15, 18 | 171 | 70% (63-77) | 31% (24-38) | 11-58% | 100% |
| EEG | | | | | | |
| α -coma pattern | 8, 9, 10, 15, 25, 35 | 453 | 66% (62-71) | 20% (16-24) | 15-43% | 71-100% |
| α -coma pattern, burst-suppression pattern, or isoelectric | 2, 9, 10, 15, 16, 32, 35, 23, 26, 29 | 638 | 67% (63-71) | 44% (40-47) | 42-84% | 71-100% |
| Burst-suppression pattern, or isoelectric | 9, 10, 11, 15, 29, 35 | 365 | 57% (52-62) | 33% (28-38) | 31-84% | 71-100% |
| Convulsions | | | | | | |
| Convulsions and/or myoclonus | 11, 18, 19, 20, 37 | 361 | 74% (69-79) | 35% (30-40) | 16-85% | 25-92% |
| Status epilepticus and/or myoclonus | 20, 28 | 221 | 68% (56-80) | 34% (32-37) | 38-67% | 96-100% |
| GCS | | | | | | |
| 3-5 in first 24 h | 14, 33, 36 | 137 | 77% (70-84) | 68% (64-83) | 63-82% | 54-100% |
| N20 | | | | | | |
| Bilateral absence on SSEP first week | 7, 11, 13, 14, 15, 19, 30, 23, 27, 33, 34 | 563 | 76% (73-80) | 33% (29-37) | 28-73% | 100% |

M1-3=motor response to pain flexion or less; M1-2=motor response to pain extension or less; M=1=no motor response to pain. GCS 3-5=score 3-5 on the Glasgow Coma Scale. EEG=electroencephalography; N20 on SSEP=early cortical response to median nerve SSEP.

Table 1: Prognostic factors

nerve stimulation, and further] present on at least one side; absent: cortical responses bilaterally absent); electroencephalographic (EEG) recordings (because the classification of α -coma pattern proved to be variable, we classified EEG recordings in three ways: α -coma pattern versus all other recordings; α -coma pattern, burst suppression pattern, or isoelectric recording versus all other recordings; and burst-suppression pattern or isoelectric recording versus all other recordings).² Outcome data were extracted as poor outcome (death or vegetative state) or good outcome (any other outcome state).³ For all data, time of assessment with respect to coma onset was documented. Both the assessment of the potentially eligible studies for meeting the entry criteria and the data extraction were done independently by EGJZ and AH. In cases of disagreement consensus was sought with the other authors.

Analyses

Analyses were done on the basis of 2×2 tables, with poor outcome (death or vegetative state) and poor prognostic test result defined

as present or absent. For each study, the prevalence of poor outcome and poor test result, as well as the sensitivity and specificity of the prognostic test were calculated. Because false-positive predictions of poor outcome are especially to be avoided, prognostic factors were considered important when they were 100% specific and consequently had a positive predictive value of 100% in each individual study (ie, all patients with poor prognostic test results died or remained in a vegetative state).

Because likelihood ratios are more stable than predictive values when prevalences of poor outcome vary, we additionally calculated positive likelihood ratios (sensitivity/1-specificity) for these prognostic factors in each study. The positive likelihood ratio expresses the odds that a poor prognostic test result would be expected in a patient with a poor outcome, as opposed to a patient with a good outcome. When there are no patients with a poor test result and a good outcome, these positive likelihood ratios are infinite. In these cases a value of 0.5 was added to each cell in the 2×2 tables for our calculations.

To assess the overall accuracy of the various prognostic tests,

| Prognostic factor | Study | Study characteristics | | | Positive test result | | Negative test result | | LR+ |
|--|-------|-----------------------|-------------|----------------|----------------------|--------------|----------------------|--------------|-------|
| | | Blinding | Prospective | Long follow-up | Good outcome | Poor outcome | Good outcome | Poor outcome | |
| Bilateral absence of N20 on SSEP in first week | 7 | - | ? | + | 0 | 7 | 9 | 9 | 8.8 |
| | 11 | - | + | + | 0 | 23 | 11 | 22 | 12.3 |
| | 13 | - | ? | ? | 0 | 30 | 5 | 15 | 8.0 |
| | 14 | - | ? | - | 0 | 4 | 2 | 4 | 3.0 |
| | 15 | + | + | + | 0 | 12 | 7 | 15 | 7.1 |
| | 19 | - | ? | + | 0 | 7 | 4 | 4 | 6.3 |
| | 23 | + | + | + | 0 | 19 | 14 | 7 | 21.7 |
| | 27 | - | ? | ? | 0 | 9 | 11 | 6 | 14.3 |
| | 30 | + | + | - | 0 | 6 | 11 | 8 | 10.4 |
| | 33 | + | + | - | 0 | 22 | 17 | 27 | 16.2 |
| 34 | + | + | - | 0 | 48 | 44 | 124 | 25.2 | |
| M=1 on GCS day 3 | 12 | - | - | - | 0 | 7 | 16 | 5 | 19.6 |
| | 15 | + | + | + | 0 | 3 | 7 | 24 | 2.0 |
| | 18 | + | + | + | 0 | 43 | 28 | 38 | 30.8 |
| Absent pupillary reactions on day 3 | 12 | - | - | - | 0 | 5 | 16 | 7 | 14.4 |
| | 18 | + | + | + | 0 | 18 | 28 | 63 | 13.1 |
| | 19 | - | ? | + | 0 | 6 | 4 | 5 | 5.4 |
| Burst-suppression or isoelectric EEG in first week | 9 | - | +/- | - | 0 | 11 | 5 | 24 | 3.8 |
| | 10 | - | ? | - | 0 | 6 | 4 | 11 | 3.6 |
| | 11 | - | + | + | 0 | 20 | 10 | 16 | 12.2 |
| | 15 | + | + | + | 2 | 16 | 5 | 7 | 2.4 |
| | 29 | - | ? | - | 0 | 42 | 28 | 8 | 48.3 |
| | 35 | - | ? | - | 0 | 25 | 104 | 21 | 113.9 |

+ = characteristic present; - = characteristic not present; ? = unknown; +/- = mixed (characteristic present for part of the population); LR+ = positive likelihood ratio.

Table 2: Prognostic factors with 100% specificity rates (except study 16 EEG): characteristics of studies and tests

| Prognostic factor | Pooled LR+ (95% CI) | Probability of poor outcome after poor prognostic test result (95% CI) | | | Number of patients with poor test result | Number of patients with both poor test results and good outcome | 95% CI of the pooled false positive test rates |
|--|---------------------|--|---------------|---------------|--|---|--|
| | | 60% prior | 75% prior | 90% prior | | | |
| Bilateral absence of N20 on SSEP first week | 12.0 (5.3–27.6) | 95% (89–98%) | 97% (94–99%) | 99% (98–99%)* | 187 | 0 | 0–2.0% |
| M=1 on GCS day 3 | 16.8 (3.4–84.1) | 96% (84–99%) | 98% (91–99%)* | 99% (97–99%)* | 53 | 0 | 0–6.7% |
| Absent pupillary reactions to light day 3 | 10.5 (2.1–52.4) | 94% (76–99%) | 97% (86–99%) | 99% (95–99%)* | 29 | 0 | 0–11.9% |
| Burst-suppression of isoelectric EEG first week† | 9.0 (2.5–33.1) | 93% (79–98%) | 96% (88–99%) | 99% (96–99%)* | 120 | 2 | 0.2–5.9% |

*Percentages over 99% were conservatively rounded off downwards. † χ^2 -test: $p=0.10$, random effect model used; for the other pooled LR+ (positive likelihood ratio) the fixed effects model could be used.

Table 3: Prognostic accuracy of the four prognostic factors in table 2: pooled results

we calculated the 95% CIs of the pooled positive likelihood ratios and the pooled false-positive test rates. Because likelihood ratios are algebraically identical to risk ratios,⁴ the data were combined accordingly.

In case the χ^2 analysis showed our data to be heterogeneous, we used the random-effects model of DerSimonian and Laird, as described by the research group of Ioannidis.⁵ If no heterogeneity could be shown, we used a fixed-effects model (Mantel-Haenszel risk-ratio method).⁶ The estimated pooled-positive likelihood ratios were also used to calculate the probability of a poor outcome after a poor prognostic test result, with three values of overall poor outcome consistent with values found in the literature as prior probabilities.

Finally, we did subgroup analyses of our main results to examine whether these could be biased by differences in study design or study populations. In this respect, the most important study characteristic is masking of the treating physicians from the test result, because patient characteristics, which are generally perceived by doctors as predictive of poor outcome (on whatever grounds), may have caused restrictions in therapeutic support, leading to poor outcome as a self-fulfilling prophecy. The following four subgroups were defined: treating physicians aware or not aware of the test results (unknown taken as aware); prospective study design versus retrospective or unknown; time of outcome assessment (at least 3 months versus less than 3 months, or unknown); and prevalence of overall poor outcome (below versus above median). Within each subgroup we recalculated the pooled positive-likelihood ratios and the pooled false-positive test rates and their 95% CIs.

Results

The literature search yielded 1667 publications, including 65 on the prognostic value of neurological and neurophysiological parameters (a list of these 65 studies is available from the author).

Of the 65 studies, 32 were excluded for the following reasons: selection of patients based on clinical features with potential prognostic value (three studies) or on specific outcomes (seven studies), inclusion of non-comatose patients (three studies), patients with coma from other causes than global anoxia-ischaemia (five studies) or young children and neonates (one study), poor definition of prognostic features or exclusive presentation of data regarding combinations of features (four studies), lack of raw data (two studies), outcome presented as death versus survival only (four studies), dual publication of same data set (one study), dual publication of overlapping data sets (two studies; only studies with largest patient population included).

Of the 33 included studies, 24 were identified from the electronic databases^{2,7–29} and nine from reference tracing.^{30–38} The included studies were focused on ten neurological and four neurophysiological factors. Descriptive data for these factors are presented in table 1.

Three factors were 100% specific in all studies—ie, no

patients had a good outcome in the presence of any of these factors: absence of pupillary reactions to light on the third day, absent motor response to pain on the third day, and bilateral absence of cortical response to median nerve SSEP within the first week. A burst-suppression or isoelectric pattern on EEG within the first week proved to be important as well because it had a 100% specificity in five out of six studies (in one study,¹⁶ with a specificity of 71%, two of 18 patients with a seriously impaired EEG had a relatively good outcome). For each study, detailed data regarding these four prognostic factors in terms of study characteristics, test results, and positive likelihood ratios are presented in table 2.

Pooled positive-likelihood ratios with 95% CI, the probabilities of poor outcome after poor test results for three prior probabilities and the 95% CIs of the pooled false-positive test rates are presented in table 3. The point estimates of the pooled positive-likelihood ratios were highest for an absent motor response to pain and the absence of SSEPs. The CI of the positive-likelihood ratio of the SSEP, however, was relatively narrow compared with that of the other factors because of the larger number of patients studied. A poor test result of each of the four prognostic factors increases the probability of poor outcome considerably. However, the relatively narrow CI for the positive-likelihood ratio of the SSEP results in the most precise estimate of the posterior probabilities. The relatively accurate prognostic value of the SSEP was also shown by the 95% CI upper limit of the pooled false positive test rate of 2%.

Additional subgroup analyses were done on the SSEP-data (table 4).

| Study characteristics | Pooled LR+ (point estimate) | Number of patients with poor test result | Number of patients with both poor test results and good outcomes | 95% CI of pooled false positive test rates |
|----------------------------------|-----------------------------|--|--|--|
| Awareness | | | | |
| Blinded | 16.3 | 107 | 0 | 0–3.4% |
| Not blinded or unknown | 8.6 | 80 | 0 | 0–4.5% |
| Type | | | | |
| Prospective | 15.6 | 130 | 0 | 0–2.8% |
| Retrospective or unknown | 7.7 | 57 | 0 | 0–6.3% |
| Follow-up | | | | |
| Long (≥ 3 months) | 11.0 | 68 | 0 | 0–5.3% |
| Short (< 3 months) or unknown | 12.9 | 119 | 0 | 0–3.1% |
| Poor outcome rate | | | | |
| High (above median) | 11.2 | 117 | 0 | 0–3.1% |
| Low (below median) | 13.0 | 70 | 0 | 0–5.1% |

LR+=positive likelihood ratio. Median poor outcome rate=78.9%

Table 4: Prognostic accuracy of the SSEP: subgroup analyses in relation to differences in study design and study population

Discussion

Our literature analysis identifies four variables that predict poor outcome in patients with anoxic-ischaemic coma with considerable accuracy: absence of pupillary light reactions on the third day, absent motor responses to pain on the third day, bilateral absence of early cortical responses to median nerve SSEP within the first week, and a burst-suppression or isoelectric pattern on EEG within the first week. Of these variables, SSEP has the smallest CIs of its pooled positive-likelihood ratio and pooled positive-test rate. In addition, evoked responses are less susceptible to metabolic changes and drugs³⁹⁻⁴² than the other variables. For the other three variables the CIs as well as their susceptibility to metabolic changes and drugs make them too unreliable to base non-treatment decisions solely on their results. Therefore, SSEP may be considered the most useful predictor of poor outcome.

Because our analysis was based only on data published in the biomedical literature the question arises whether publication bias may have influenced our main conclusions. Regarding the large number of publications reporting poor-to-moderate prognostic values of many variables such a bias seems unlikely. In six of the 32 excluded studies the prognostic value of SSEP was studied. In one study,⁴² two patients with absent SSEPs were reported to have recovered consciousness; the SSEPs, however, were done within the first 24 h. In the other five studies, all patients with absent SSEPs died or remained in a vegetative state.

The predictive value of combinations of variables has been analysed in several studies, but since these combinations differed between studies, they could not be included in our analysis. We also could not address the mutual independence of the single variables. It remains uncertain whether patients with more than one poor test result have a larger probability of poor outcome than patients with a single poor test result.

In our analysis, we combined death and vegetative state as poor outcome. Because follow-up was only 1 month in several studies and patients who are then in a vegetative state may still recover consciousness, it may be questioned whether this period is long enough to justify this combined outcome measure. Late recovery, with severe mental and motor disability in most patients, has been reported in 11% of patients who have been in non-traumatic coma for 1 month.⁴³ This percentage is derived from patients with several kinds of non-traumatic coma, and refers to all patients comatose after 1 month, irrespective of the status of predictive variables such as SSEP. In our analysis, 179 of the 187 patients with absent N20-responses died during follow-up. The remaining eight (4%) were in a vegetative state at the end of follow-up. In studies with a 6-month follow-up none of the patients who were in a vegetative state after 1 month had recovered consciousness at 6 months.^{7,11} In one study not included in our analysis, 31 patients with non-traumatic coma for at least 2 months were followed up for at least 8 months. Recovery of consciousness did not occur in any of the 17 patients in whom cortical SSEPs were absent.⁴⁴ Taken together, these observations suggest that the chance of recovery of consciousness in patients with absent N20-responses in the first week who are in a vegetative state after 1 month is virtually nil. We therefore conclude that the vegetative state after 1 month in patients with absent cortical SSEPs indicates irreversible brain damage, severe enough to justify its combination with death as one outcome measure.

Although our SSEP-data were only derived from unselected series of patients, clinical heterogeneity cannot be completely ruled out. The latter was suggested by the variations in overall poor outcome from 56% to 90% and in the sensitivities of the poor SSEP test result for poor outcome from 28% to 73%. The differences in poor-outcome rates, however, did not affect the results of our analysis. Moreover, variations in sensitivities are less important because our main interest is in highly specific variables, whereas by calculating likelihood ratios we took sensitivities into account.

In contrast to our expectation, the three other subgroup analyses showed higher pooled positive-likelihood ratios for the studies in which the clinicians were blinded, for prospective studies, and for studies with shorter follow-up periods, compared with the studies with opposite characteristics. These latter studies were relatively small, which leads to an underestimation of specificity, and therefore also of positive-likelihood ratio, given the mathematical correction we used.

The non-significant differences between the CIs of the false-positive test rates can be explained by the differences in sample sizes between the subgroups.

Our finding that the absence of cortical SSEPs is a more useful predictor of poor outcome than most clinical variables is in accordance with the pathophysiology of anoxic-ischaemic brain damage. The cerebral cortex is always the most severely damaged structure, whereas brainstem structures remain intact in all but the most afflicted patients.^{45,46} Because early cortical responses after median nerve stimulation are generated in the somatosensory cortex,⁴⁷ recording of SSEPs will identify more patients with severe brain damage than testing brainstem reflexes alone. The poor prognosis of patients whose brainstem reflexes are still absent at day 3 is explained by the fact that brainstem failure in this condition necessarily implies severe cortical damage.

In conclusion, our analysis of the literature has provided more prognostic certainty in patients with anoxic-ischaemic coma than the separate studies of prognostic variables could offer. We believe that bilateral absence of early cortical responses to median-nerve stimulation in the first week of coma predicts death or a vegetative state with enough confidence to allow decisions to stop treatment to be based on this information. Accordingly, based on this conclusion and on additional considerations, we suggest the following clinical guidelines:

In patients with anoxic-ischaemic coma, considerations regarding neurological outcome are postponed until 72 h after the onset of coma. This is motivated by our finding that the prognostic value of several clinical variables is more accurate after 72 h than on the first day of coma, and by the finding of Guérit and colleagues⁴² that two patients with absent SSEPs during the first 24 h recovered consciousness. Both findings could be explained by the assumption of a shock phase early after the insult from which the brain can partly recover, as has been observed in other conditions.⁴⁸

After 72 h, patients with either absent pupillary light reflexes or motor response to pain no better than flexion will undergo SSEP-testing. This selection on clinical grounds is proposed to exclude a possibly non-existent group of patients in whom the clinical condition would seem to be in contrast to a poor test result on SSEP. Few clinicians would feel comfortable to withdraw treatment in such patients. SSEPs should be done and interpreted by an

expert, and if there is a clinical suspicion of additional focal brain damage, this should be excluded before SSEP is interpreted.

In patients in whom early cortical SSEP-responses are bilaterally absent after this procedure further treatment will be regarded futile and only palliative care will be given.

We are aware that with these guidelines, only a subgroup of irrecoverable patients can be identified. Clinical treatment decisions for the remaining patients can only be improved by additional evidence from further clinical research.

Contributors

A Hijdra initiated and supervised the study, and with C P Stoutenbeek, R J de Haan, and E G J Zandbergen designed the study protocol. EGJZ collected the data and with RJdeH did the analyses. J H T M Koelman interpreted the clinical neurophysiological data. EGJZ, RJdeH, and AH wrote the paper. All authors contributed to the final manuscript.

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