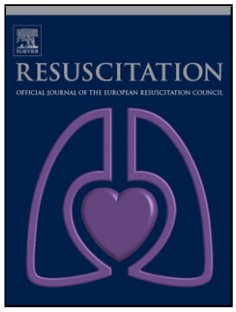
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Late awakening, prognostic factors and long-term outcome in out-of-hospital cardiac arrest – results of the prospective Norwegian Cardio-respiratory Arrest Study (NORCAST)

Espen R. Nakstad, Henrik Stær-Jensen, Henning Wimmer, Julia Henriksen, Lars Alteheld, Antje Reichenbach, Tomas Drægni, Jūratė Šaltytė Benth, John Aage Wilson, Lars Etholm, Miriam Øijordsbakken, Jan Eritsland, Ingebjørg Seljeflot, Dag Jacobsen, Geir Ø. Andersen, Christofer Lundqvist, Kjetil Sunde

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Late awakening, prognostic factors and long-term outcome in out-of-hospital cardiac arrest – results of the prospective Norwegian Cardio-respiratory Arrest Study (NORCAST)

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ABSTRACT

BACKGROUND: Outcome prediction after out-of-hospital cardiac arrest (OHCA) may lead to withdrawal of life-sustaining therapy if the prognosis is perceived negative. Single use of uncertain prognostic tools may lead to self-fulfilling prophecies and death. We evaluated

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prognostic tests, blinded to clinicians and without calls for hasty outcome prediction, in a prospective study.

METHODS: Comatose, sedated TTM 33-treated OHCA patients of all causes were included. Clinical-neurological/-neurophysiological/-biochemical predictors were registered. Patients were dichotomized into good/poor outcome using cerebral performance category (CPC) six months and > four years post-arrest. Prognostic tools were evaluated using false positive rates (FPR).

RESULTS: We included 259 patients; 49% and 42% had good outcome (CPC 1–2) after median six months and 5.1 years. Unwitnessed arrest, non-shockable rhythms, and no-bystander-CPR predicted poor outcome with FPR (CI) 0.05 (0.02–0.10), 0.13 (0.08–0.21), and 0.13 (0.07–0.20), respectively. Time to awakening was median 6 (0–25) days in good outcome patients. Among patients alive with sedation withdrawal >72h, 49% were unconscious, of whom 32% still obtained good outcome. Only absence of pupillary light reflexes (PLR) -and N20-responses in somato-sensory evoked potentials (SSEP), as well as increased neuron-specific enolase (NSE) later than 24h to >80μg/L, had FPR 0. Malignant EEG (burst suppression/epileptic activity/flat) differentiated poor/good outcome with FPR 0.05 (0.01–0.15).

CONCLUSION: Time to awakening was over six days in good outcome patients. Most clinical parameters had too high FPRs for prognostication, except for absent PLR and SSEP-responses >72h after sedation withdrawal, and increased NSE later than 24h to >80μg/L.

Keywords: out-of-hospital cardiac arrest; prognostication; sedation; targeted temperature management; withdrawal of life-sustaining therapy; cerebral performance category; Glasgow coma scale; neuron-specific enolase; EEG; SSEP.

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BACKGROUND

Survival after out-of-hospital cardiac arrest (OHCA) has improved over the last decades in health care systems with good chains of survival[1, 2]. Among patients with return of spontaneous circulation (ROSC), up to 50% may be discharged neurologically intact[3, 4]. Outcome prediction is still difficult since many patients remain unconscious due to brain damage, reversible metabolic disturbances or sedative effects[5-7].

There is still fear among clinicians that some patients may end up in a vegetative state if they survive cardiac arrest. This assumption may lead to withdrawal of life-sustaining therapy (WLST) if the prognosis is perceived negative. In the western world, WLST applies to more than 50% of deaths in OHCA patients[3, 8-10]. Unfortunately, too early prognostication using single, uncertain tests in sedated comatose patients treated with targeted temperature management (TTM) increases the risk of self-fulfilling prophecies, WLST and death[9-11].

The overall objective of the Norwegian Cardio-Respiratory Arrest Study (NORCAST – NCT 01239420) was to explore prognostication in patients with persisting coma through a design where clinicians were blinded to diagnostic tests, under an otherwise unchanged treatment regime without no calls for hasty outcome prediction or early WLST. The main aim was to assess the ability of currently recommended diagnostic tools[12, 13] to identify patients with a poor prognosis (defined as cerebral performance category (CPC) score 3–5) after six months. Secondary aims were to evaluate long-term outcome more than four years after OHCA as well as clinical, neurophysiological, and biochemical variables associated with neurological outcome.

METHODS

Study population and setting

In this prospective observational study we included adult (>18 years of age) comatose (Glasgow coma scale (GCS) <9) OHCA patients of cardiac and non-cardiac causes with stable

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ROSC (>20 min), admitted to Oslo University Hospital Ullevål (OUHU) between October 1st 2010 and January 30th 2014. Exclusion criteria were; OHCA following trauma/acute onset intra-cerebral pathology, cardiopulmonary resuscitation (CPR) <5 min followed by spontaneous awakening, OUHU admission >6 hours (h) after OHCA, and treatment withdrawal in the emergency room (based on an abstain-from-resuscitation wish, terminal cancer disease, or very advanced age/dementia). Inclusion was paused during public holidays due to logistical restrictions. OUHU is a community and regional hospital with over 45.000 yearly admissions.

Treatment protocol

All patients received conventional care in accordance with our standard operating procedures (SOPs)[3]. Immediate coronary angiography was performed if a cardiac cause of arrest was suspected, with subsequent percutaneous coronary intervention (PCI) on indication. TTM was initiated (33 °C for 24h, TTM-33), using ice-cold fluids/ice-packs and external cooling (Arctic Sun, Bard Medical, US). Patients were treated mainly in two medical ICUs.

During TTM-33, normo-oxygenation and -ventilation were targeted. All patients were sedated under the hospitals´ protocol for post-resuscitation care, recommending fentanyl (1–6 μg/kg/h) and midazolam (0.1–0.6 mg/kg/h) in unstable patients (defined as middle arterial pressure (MAP) <65 mmHg and >0.1 μg/kg/h of norepinephrine), and fentanyl (1–6 μg/kg/h) and propofol (1–4 mg/kg/h) in stable patients. Richmond agitation sedation score (RASS) 5 (unarousable) was targeted. During rewarming, sedation was withdrawn at 36 °C if the clinical condition allowed for it.

Study investigations

GCS, pupillary light reflexes (PLR), and use of sedatives were registered daily by attending nurses and physicians in all comatose patients, also after referral to local hospitals. These data were accessible to those performing the registrations.

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Blood samples were drawn on admission and one, two, three, five and seven days after OHCA for serum neuron-specific enolase (NSE) analyses, using an in-house immunoradiometric assay[14]. Samples with strong haemolysis were excluded.

Electroencephalography (EEG) and somato-sensory evoked potential (SSEP) for N20 responses were registered, to the extent possible, 72h after discontinuation of TTM-33 in all comatose patients (Figure 1). Two senior neurophysiologists independently interpreted the registrations, blinded from medical history details. If evaluations differed, a third specialist had the deciding vote. For EEG analyses, a five graded scoring system was used[15] (Figure 1).

Outcome assessment

Primary outcome was assessed six months after OHCA by two experienced neurologists, using standardized clinical examination and CPC[16, 17] to dichotomize patients into good (CPC 1-2) or poor (CPC 3-5) outcome. Secondary outcome was CPC >4 years after OHCA. Data from local hospitals, general practitioners, questionnaires, and telephone interviews were used to assess CPC scores in the few patients unable to meet.

Finally, clinical, neurophysiological and biochemical variables were analyzed, using GCS level >72h after sedation withdrawal. A study committee considered all causes of death and WLST decisions based on data from medical journals.

Blinding

Prior to study initiation, the treating staff were informed about the purpose of the study and a business-as-usual approach was emphasized, with unchanged SOPs and no calls for hasty outcome prediction or early WLST. Our routine prognostication tools at that time were mainly multidisciplinary decisions based on neurological assessment, with only occasional use of NSE, SSEP, and EEG.

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Sampling of prognostic markers was performed by two study investigators with results blinded to clinicians. The investigators did not discuss any test results with the treating staff, but clinicians were allowed to request non-blinded investigations at their own discretion. They were also informed of any study EEGs revealing epileptic activity and could have individual SSEP results un-blinded, if specifically requested.

Ethics and data management

The study complies with the Helsinki Declaration and was approved by the Regional committee of medical ethics in Norway (Approval REK-S-O/A-2010/1116a). Written informed consent was obtained from close relatives or guardians within 24h after hospitalization and from all patients regaining consciousness and decision-making capacity within six months.

Clinical, biochemical and outcome data were prospectively collected from medical records, questionnaires, and paramedic records[18].

Statistics

Patient characteristics and prognostic tools were described by means and standard deviations (SD), and medians and min-max values, for continuous variables, as appropriate, and frequencies and percentages for categorical variables. Patient groups defined as CPC 1–2 and CPC 3–5 were compared by independent samples t-test and χ^2-test. Independent samples t-test was applied for comparison of all continuous variables, also skewed ones, as the conclusion is little affected by departures from normality for large samples.

To assess the prognostic ability of various diagnostic tools, we calculated the false positive rate (FPR) as the ratio between the number of patients with good outcome falsely classified as poor outcome, and the total number of patients with good outcome, at six months. The 95% confidence interval (CI) for FPR was calculated. Data were analyzed using IBM SPSS

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Statistics Version 25 for Windows (IBM, Armonk, New York, USA). Results with p-values below 0.05 were considered statistically significant.

RESULTS

Patient characteristics

Among 297 comatose patients considered, 259 were included in the study (Figure 2). Follow-up investigations were performed after median 6.0 (5.5–6.6) and 61.8 (48.0–91.5) months, respectively, until May 8th 2018.

The majority of patients had a witnessed arrest (88%) of presumed cardiac cause (81%). Initial ventricular tachycardia/fibrillation (VT/VF) was present in 68% of the patients and the bystander CPR rate was 86% (table 1). Mean time from OHCA to ROSC was 27.3 (SD 18.4) min, significantly shorter in those with good vs. poor outcome (22.2 vs. 33.0 min, respectively, $p<0.001$) (Table 1). Target temperature was not reached in 15 patients.

Outcome data

Overall six-month survival rate was 53%, with 49% obtaining good outcome (Figure 2, Table 1). Causes of death were brain injury (65%), cardiac instability (23%) and other/unknown causes (12%). WLST was initiated median 13 (0–65) days after admission in 71 (27%) patients (i.e. 59% of non-survivors) (Figures 2 and 3C). In 10 patients with a cerebral cause of death, WLST was initiated already 2-7 days after admission. All these patients had signs of severe cerebral injury (absent brain stem reflexes and/or clinical signs of cerebral herniation verified by brain imaging), in addition to multi-organ failure (Additional Supplementary Materials, ASM).

After median 5.1 (4.0–7.6) years, 45% were still alive, 42% with good outcome. No patients were in CPC 4 (Figure 2), and descriptive data did not differ between the two outcome time points except for age, which at >4 years was significantly lower for good vs. poor outcome (means 58.5 (SD 12.1) vs. 63.4 (SD 14.7) years, respectively ($p=0.005$)) (not tabulated). Among

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10 CPC 3 patients (Figure 2), the CPC score after >4 years was unchanged in four, improved in two (CPC 2), and worsened in four patients (CPC 5), respectively.

Time from arrest to permanent sedation withdrawal did not differ between CPC 1–2 and CPC 3 patients; (mean (SD, min-max) 5.4 (7.5, 1–60) and 4.7 (2.8, 1–8) days, respectively (NS)). Time from arrest to awakening was 6.1 (4.0, 0–25) and 16.9 (10.6, 7–36) days ($p<0.001$), respectively (Figure 3A). Among 185 patients still alive with sedation withdrawal >72h, 91 (49%) were still unconscious, of whom 32% eventually obtained good outcome (Figure 3B).

Best CPC obtained among all patients regaining consciousness was CPC 1 (n=116), CPC 2 (n=18), and CPC 3 (n=22), of whom 18 patients died (eight patients with WLST) within six months due to new or worsening disease (Figure 3C).

Predictors for outcome

The strongest pre-hospital predictors for poor outcome were unwitnessed arrest, non-shockable rhythms, and no-bystander CPR, with FPRs from 0.05 to 0.13, whereas time to ROSC >25 min had FPR 0.32 (0.24–0.42) (Table 3).

In-hospital tests strongly differentiating poor from good outcome >72h after sedation withdrawal were; absence of PLR and increased NSE later than 24h to >80μg/L (both FPR 0), whereas GCS<9 and GCS-M 1-3 had FPRs of 0.24 and 0.27, respectively (Table 3). NSE values were significantly different in poor vs. good outcome patients ($p<0.001$) both for maximum NSE, and at 24h and 48h (Table 2). A scatterplot of all obtained NSE values at different time points with respective CPC scores is shown in Figure 4. Single maximum values over 60 and 80 μg/L had FPRs of 0.07 and 0.02, respectively (Table 3).

Malignant EEG (grade 4–5) differentiated poor from good outcome with FPR 0.05, whereas absence of SSEP N20-responses had FPR 0 (Table 3). Altogether 68 SSEP registrations were undertaken, but 28 were inconclusive or had too poor quality for interpretation.

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DISCUSSION

In this prospective study of 259 comatose, deeply sedated TTM-treated OHCA patients, results of prognostic tests were blinded to clinicians to avoid hasty WLST decisions and self-fulfilling prophecies. Good outcome was present in 49% and 42% after six months and five years, respectively. Time to awakening was more than six days in patients with good outcome, and 32% of patients still comatose >72h after sedation withdrawal survived with good outcome. Although 58% of all non-survivors had WLST, this was initiated median 13 days after admission, emphasizing that our objective to avoid hasty WLST decisions affecting study end-points seems justified.

Currently, a multimodal prognostication protocol is recommended, which should be initiated 3-5 days after cardiac arrest in still comatose patients[13]. This protocol has, to our knowledge, never been tested in prospective trials. Zhou et al. documented in a retrospective study in 226 patients that the protocol had an FPR of 0 at six months. However, survival was lower than in the present study, and the sensitivity for poor outcome detection at six months was only 28%[19]. Noteworthy, in a recent survey, 640 attending respondents considered no more than 0.1% as an acceptable FPR for WLST[20]. Importantly, premature WLST decisions will also inevitably increase mortality (and improve FPR) in retrospective studies[9, 10].

Although multimodal prognostication is recommended[12, 13], many clinicians still rely on clinical signs in their treatment decisions. The present data showed that easily accessible prognostic tools gave FPRs too high for practical use. As an example, GCS<9 would have led to WLST in 29 good outcome patients if used alone for prognostication >72h after sedation withdrawal. The use of GCS motor response score 1-3 at this time would have led to WLST in 25 good outcome patients. Noteworthy, current ERC guidelines recommend GCS-M 1-2 as cut-off for prognostication[12].

Other frequently used predictors for early WLST, such as time to ROSC and witnessed/unwitnessed arrest, are often subject to uncertainty and incorrect reporting at the time

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of admission. Based on the current data, asystole/PEA, unwitnessed arrest, and time to ROSC >25 min, gave 17, 5, and 37 false positives, respectively. The only clinical variable predicting poor outcome with FPR 0 was absence of PLR. However, only 6% of all comatose patients had absent PLR, reflecting presence of brain stem function in many poor outcome patients[5], thereby limiting utility. In addition, scores based on responses to external stimuli will likely depend on sedatives.

NSE is affected by many factors, including haemolysis, and the optimal way to use it is under debate[12, 13, 21, 22]. According to current guidelines, NSE levels above 60 μg/l measured 48–72h after ROSC are very rarely associated with good outcome[13]. Although some advocate 24–48–72–hour ratios[23, 24], it is unclear whether serial measurements further improve prognostication[25]. Our data indicate that a WLST policy for NSE exceeding 80 μg/l would have led to loss of three patients with good outcome perspectives. With these precautions in mind, and considering the previously mentioned 0.1% limit for acceptable FPR[20], we found rates sufficiently low for practical clinical use only when NSE continued to increase later than 24h in patients with maximum NSE >80μg/L.

EEG and SSEP registrations 72h after sedation withdrawal are also recommended in prognostication protocols[12, 13, 21]. Similar to previous findings[13, 26, 27], bilateral absence of N20 responses in SSEP gave FPR 0, but the signals could only be interpreted in 40 registrations with only eight showing bilaterally absent responses. SSEP was clearly limited by logistical challenges, use of intravenous cannulas in the proximity of the median nerve, electrical interference, and early referral to local hospitals. SSEP is also user dependent, with large inter-observer variability[26, 28].

Assessment of EEG is often subjective and consensus-based, and criteria for prognostication vary[13, 29, 30]. Using predefined EEG grading, we could differentiate poor from good outcomes with FPR 0.05. This still would have led to WLST in three good outcome patients if EEG had been used as a single prognostic tool. However, these three patients all had responsive

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PLRs. As with SSEP, EEG may for technical and logistical reasons not be possible to obtain in some patients.

Our study indicates that attempts to prognosticate too early could lead to WLST in patients with good recovery potential. From a practical point of view, it seems appropriate to use a combination of clinical assessment, PLR, GCS, EEG, NSE and SSEP, provided that timing of sedation withdrawal is taken thoroughly into account. Therefore, patience is needed and clinicians must be willing to continue treatment beyond currently recommended time points for prognostication.

Noteworthy, 15% of patients died after initial awakening, which is higher than reported in a recent multicenter cohort (4%)[31], and may be explained by our longer observation time. It is crucial to report these numbers when evaluating prognostication tools, due to their influence on results and overall interpretation.

Limitations and strengths

This was a single-centre observational study, which limits generalizability. However, it allowed investigators to follow the same patients over time. Since all patients were treated with the same TTM-33 protocol, confounders based on quality of care were minimized.

In accordance with the study protocol, 72h NSE values were made available to clinicians who would likely have requested the same test. Although the result was usually not available during the first week of treatment, we cannot entirely rule out that it was considered by some clinicians. Additional biomarker analyses, and use of pairs or combinations of predictors, could possibly have further strengthened our study[32].

Even if SSEP was not reported as a reason for WLST in any of the study patients, blinded SSEP results were requested by clinicians in 11 cases. Hence, the assessment of SSEP as a diagnostic tool was clearly limited in our study. It should also be noted that we used an EEG classification[15] available at study initiation in 2010 which differs from current ERC guidelines[12].

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Consequently, some EEG patterns classified as grade 4 would not have been regarded malignant by newer classification [29].

Sedation regimen affect time to awakening and WLST[33], and was highlighted as a knowledge gap in the 2014 ERC/ESICM advisory statement[13]. Our sedation protocol recommended propofol/fentanyl in stable patients, but the majority were deeply sedated (RASS 5) with midazolam/fentanyl (Table A1, ASM). Although we do not have the total doses used, they were probably higher than previously reported [6, 34], based on the sedation protocol recommendations and clinical experience. However, neurophysiological tests and standardized clinical assessments were done >72h after sedation withdrawal. Whether our sedation regimen is an advantage or disadvantage in terms of brain recovery remains unclear, but it clearly affects time to awakening[7].

Depth of hypothermia affects pharmacokinetics of sedatives[35], and in the TTM trial, TTM-36-patients woke up earlier than TTM-33-patients ([36]supplementary material). Thus, sedation and TTM depth should be taken into account when decisions on discontinuation of treatment are made.

We cannot entirely rule out that self-fulfilling prophecies were present in some of the ten patients dying from cerebral causes after WLST initiation during the first week of treatment. Although they all had early signs of severe cerebral injury, in addition to multi-organ failure, cerebral angiography was not performed in all these patients.

Finally, quality of life analyses are recommended as important outcome endpoints[37, 38], but fall outside the scope and main objectives in the present study.

CONCLUSIONS

Survival with good outcome was 49% among comatose OHCA patients, and 42% had a good outcome after median 5.1 years. Most clinical parameters had too high FPRs for prognostication, except for absent PLR and SSEP-responses >72h after sedation withdrawal, and

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increased NSE later than 24h to >80μg/L. Time to awakening was more than six days in good outcome patients, and among patients still comatose >72h after sedation withdrawal, one of three had a good outcome.

CONFLICTS OF INTEREST

The are no conflicts of interests to declare.

The authors declare that they have no conflicts of interests.

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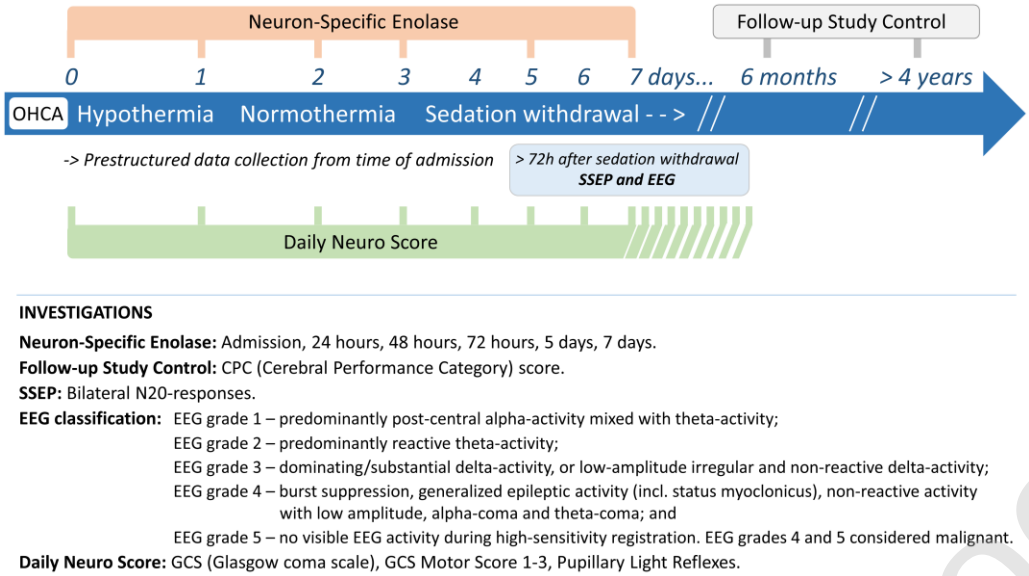
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LEGENDS TO FIGURES



INVESTIGATIONS

Neuron-Specific Enolase: Admission, 24 hours, 48 hours, 72 hours, 5 days, 7 days.
Follow-up Study Control: CPC (Cerebral Performance Category) score.
SSEP: Bilateral N20-responses.
EEG classification: EEG grade 1 – predominantly post-central alpha-activity mixed with theta-activity;
EEG grade 2 – predominantly reactive theta-activity;
EEG grade 3 – dominating/substantial delta-activity, or low-amplitude irregular and non-reactive delta-activity;
EEG grade 4 – burst suppression, generalized epileptic activity (incl. status myoclonicus), non-reactive activity with low amplitude, alpha-coma and theta-coma; and
EEG grade 5 – no visible EEG activity during high-sensitivity registration. EEG grades 4 and 5 considered malignant.
Daily Neuro Score: GCS (Glasgow coma scale), GCS Motor Score 1-3, Pupillary Light Reflexes.

Figure 1 – Study Design
Main data collection time points. OHCA, out-of-hospital cardiac arrest, SSEP, somato-sensory evoked potential, EEG, electroencephalography. EEG grades 1-5 refer to the study EEG classification system.

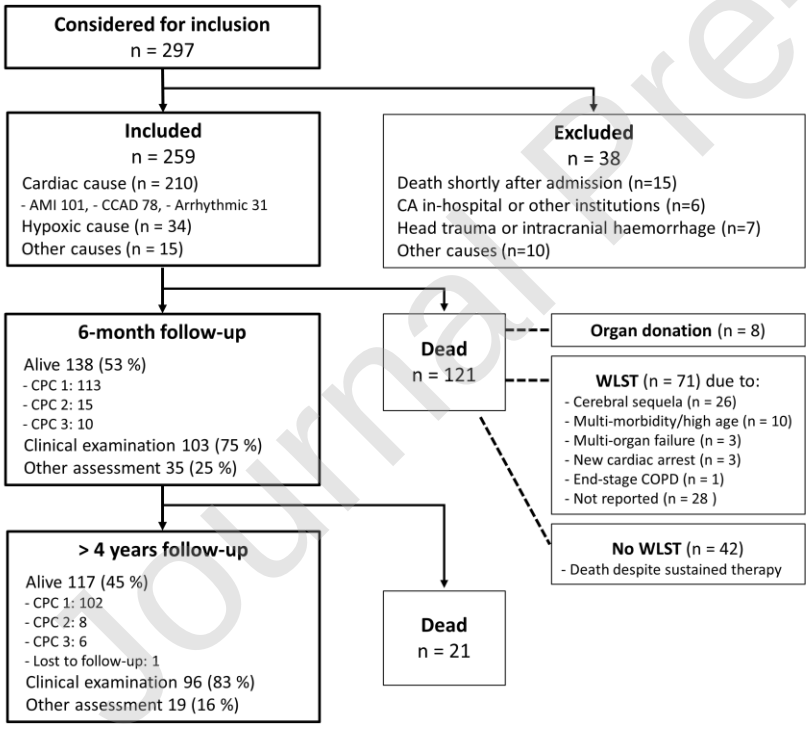


Figure 2 – STROBE flow chart of the NORCAST trial
Patients included in the NORCAST trial. AMI, acute myocardial infarction, CCAD, chronic coronary artery disease, Arrhythmic, primary arrhythmic arrest, CA, cardiac arrest, CPC, cerebral performance category, WLST, withdrawal of life-sustaining therapy, COPD, chronic obstructive pulmonary disease.

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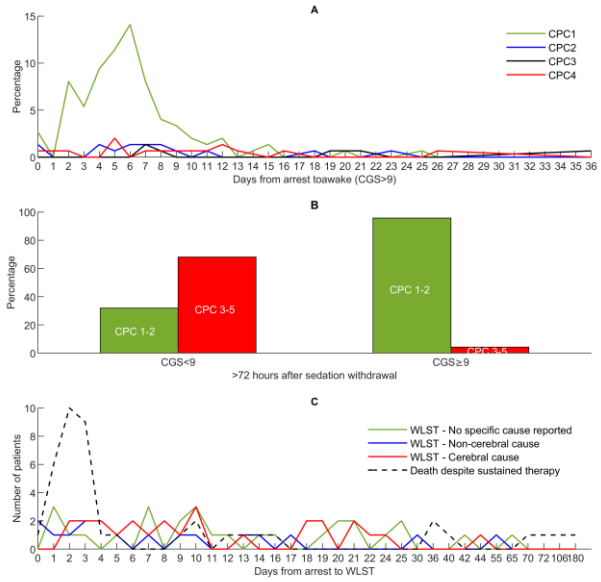


Figure 3 – Time to awakening

A) Days from cardiac arrest to awakening (GCS≥9) in patients with good (CPC 1–2) and poor (CPC 3–5) outcome six months after hospital admission. Mean number of days to awakening for patients with CPC 1 (green), CPC 2 (blue), CPC 3 (black), and 5 (red) were 6.1, 7.7, 16.9, and 8.9 days, respectively. Eighteen patients who initially regained consciousness (red line) later died due to new or worsening disease (time-lines missing in two patients); their best post-ICU score was CPC 1 (n=3), CPC 2 (n=3), and CPC 3 (n=12), respectively. No patients were in a vegetative state (CPC 4) after six months.

B) Outcome six months after hospital admission in patients with cardiac arrest, according to GCS score >72h after sedation withdrawal. Good outcome was obtained in 32% of unconscious patients and in 96% of awake patients.

C) Days from cardiac arrest to withdrawal of life-sustaining therapy (WLST) according to main causes of withdrawal; cerebral cause (red, n=26), non-cerebral cause (blue, n=17), and no specific cause reported (green, n=28). For patients who died within six months despite maximum efforts, the number of days from arrest to death are shown with stapled lines (sustained therapy, n=42). Organ donor patients (n=8) are not depicted.

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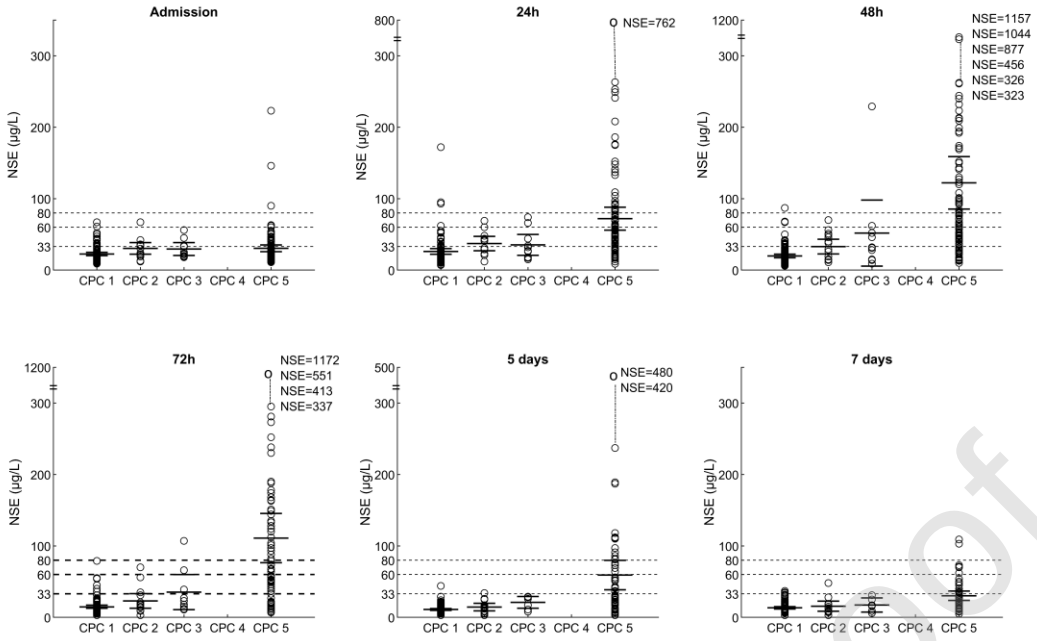


Figure 4 – Neuron-specific enolase

Neuron-specific enolase (NSE) (µg/L, mean (CI)) during the first seven days in hospital, stratified by CPC score six months post-arrest. Measurements exceeding 300 µg/L are listed next to the vertical stapled lines. The number of good-outcome patients with NSE exceeding 33, 60, and 80 µg/L (horizontal stapled lines) at any time point, was 84, 8, and 3, respectively.

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Table 1 – Patient characteristics

Patient characteristics stratified by best CPC at primary outcome assessment six months post-arrest. RA, respiratory arrest, CA, cardiac arrest, CPR, cardiopulmonary resuscitation, VT, ventricular tachycardia, VF, ventricular fibrillation, PEA, pulseless electrical activity, cath. lab, catheterization laboratory, Tp., temperature, TTM, target temperature management, EMS, emergency medical services.

		6 months		
	All patients (N=259)	**CPC1–2 (N=128)**	**CPC3–5 (N=131)**	**p-value**
Patient characteristics				
Age, Mean (SD)	61.2 (13.9)	59.7 (12.4)	62.6 (15.1)	0.095 [a]
Gender, Male, N (%)	214 (83)	111 (87)	103 (79)	0.086 [b]
Cause of arrest, N (%)				
Cardiac	210 (81)	114 (89)	96 (73)	0.005 [b]
Hypoxic	34 (13)	10 (8)	24 (18)	
Other/unknown	15 (6)	4 (3)	11 (8)	
Witnessed arrest, N (%)	228 (88)	122 (95)	106 (81)	<0.001 [b]
Bystander CPR, N (%)*	202 (86)*	104 (87)*	98 (85)*	0.628 [b]
Initial heart rhythm, N (%)				
Initial VT/VF	176 (68)	107 (84)	69 (53)	<0.001 [b]
Initial asystole/PEA	83 (32)	21 (16)	62 (47)	
Time-intervals (minutes), Mean (SD)				
CA to first shock	13.3 (8.6)	11.3 (5.6)	16.7 (11.2)	0.002 [a]
CA to ROSC	27.3 (18.4)	22.2 (16.0)	33.0 (19.3)	<0.001 [a]
Directly to cath. lab, N (%)	228 (88)	120 (94)	108 (82)	0.005 [b]
First registered Tp (Celsius), Mean (SD)	34.5 (1.3)	34.8 (1.4)	34.3 (1.3)	0.001 [a]
TTM 33 ^{0}C reached, N (%)	244 (94)	121 (95)	123 (94)	0.826 [b]

[a] Independent samples t-test; [b] χ^2-test. P-values refer to CPC 1–2 vs. 3–5.

* n=234 due to exclusion of EMS witnessed arrest (n=25).

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Table 2 – Prognostic tools

Prognostic tools stratified by best CPC at primary outcome assessment six months post-arrest. NSE, neuron-specific enolase, GCS, Glasgow coma scale, GCS-M, Glasgow coma scale – motor score, SSEP, somato-sensory evoked potential, EEG, electroencephalography.

		6 months		
	All patients	**CPC 1–2**	**CPC 3–5**	**p-value**
	(N=259)	(N=128)	(N=131)	
NSE (μg/L), Mean (SD)				
NSE highest value	82.0 (139.3)	31.9 (20.1)	131.3 (182.5)	<0.001[a]
NSE at 24 hours	47.8 (63.4)	27.2 (20.5)	68.6 (82.5)	<0.001[a]
NSE at 48 hours	65.7 (129.9)	21.2 (14.7)	116.8 (176.7)	<0.001[a]
Cerebral assessment >72h after sedation N (% of examined patients)				
	(N=185)	(N=119)	(N=66)	
GCS < 9	91 (49)	29 (24)	62 (94)	<0.001[b]
GCS-M score 1-3	72 (49)	25 (27)	47 (90)	<0.001[b]
Pupillary light response absent	10 (6)	0	10 (23)	<0.001[b]
SSEP bilateral N20 absent	(N=50)	(N=19)	(N=31)	
Yes	8 (16)	0	8 (26)	0.009 [b]
No	32 (64)	17 (90)	15 (48)	
Inconclusive	10 (20)	2 (11)	8 (26)	
EEG, N (%)	(N=107)	(N=60)	(N=47)	
Grade 1–3	76 (71)	57 (95)	19 (40)	<0.001[b]
Grade 4–5	31 (29)	3 (5)	28 (60)	

[a] Independent samples t-test; [b] χ^2-test. P-values refer to CPC 1–2 vs. 3–5.

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Table 3 – Predictors for poor outcome

Variables predicting poor cerebral outcome six months post-arrest, with false positive rates (FPR) (patients with missing data excluded from calculations). PEA, pulseless electrical activity, CPR, cardiopulmonary resuscitation, ROSC, return of spontaneous circulation, GCS-M, Glasgow coma scale – motor score, EEG, electroencephalography, SSEP, somato-sensory evoked potential, NSE, neuron-specific enolase, TP, true positives, FP, false negatives, TN, true negatives, FN false negatives.

Variables predicting poor outcome (CPC 3-5)					**6 months**
	TP	FP	TN	FN	FPR (CI)
Initial asystole/PEA (n=259)	60	71	111	17	0.13 (0.08-0.21)
Unwitnessed arrest (n=259)	25	6	106	122	0.05 (0.02-0.10)
No bystander CPR (n=234)	17	15	98	104	0.13 (0.07-0.20)
Time to ROSC > 25 min (n=219)	66	37	78	38	0.32 (0.24-0.42)
GCS < 9 * (n=185)	62	29	90	4	0.24 (0.17-0.33)
GCS-M score 1-3 * (n=146)	47	25	5	69	0.27 (0.18-0.37)
EEG grade 4-5 (n=107)	28	3	19	57	0.05 (0.01-0.15)
Pupillary light responses absent * (n=158)	10	0	114	34	0
SSEP bilateral N20 absent (n=50)	8	0	17	15	0
NSE highest value > 33 μg/L (n=258)	104	44	84	26	0.34 (0.26-0.43)
NSE highest value > 60 μg/L (n=258)	72	9	119	58	0.07 (0.03; 0.13)
NSE highest value > 80 μg/L (n=258)	57	3	125	73	0.02 (0.01-0.07)
NSE increases after 24 h (n=225)	75	38	31	81	0.32 (0.24-0.41)
NSE increases after 24 h and exceeds 60 μg/L (n=69)	53	1	8	7	0.13 (0.01-0.53)
NSE increases after 24 h and exceeds 80 μg/L (n=50)	44	0	4	2	0

n = number of study patients with valid test result

* >72h after confirmed sedation withdrawal

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