



Clinical paper

Head computed tomography for prognostication of poor outcome in comatose patients after cardiac arrest and targeted temperature management[☆]



Marion Moseby-Knappe^{a,*}, Tommaso Pellis^b, Irina Dragancea^a, Hans Friberg^c,
Niklas Nielsen^d, Janneke Horn^e, Michael Kuiper^f, Andrea Roncarati^g, Roger Siemund^h,
Johan Undénⁱ, Tobias Cronberg^a, the TTM-trial investigators

^a Lund University, Skane University Hospital, Department of Clinical Sciences, Division of Neurology, Lund, Sweden

^b Department of Anaesthesia and Intensive Care, Azienda Ospedaliera G. Panico, Tricase, Italy

^c Lund University, Skane University Hospital, Department of Clinical Sciences, Division of Anaesthesiology and Intensive Care, Lund, Sweden

^d Lund University, Helsingborg Hospital, Department of Clinical Sciences, Division of Anaesthesiology and Intensive Care, Lund, Sweden

^e Department of Intensive Care, Academic Medical Center, Amsterdam, Netherlands

^f Department of Intensive Care, Medical Center Leeuwarden, Leeuwarden, Netherlands

^g Department of Anesthesia, Intensive Care and Emergency Medical Service AAS 5, Santa Maria Degli Angeli Hospital, Pordenone, Italy

^h Lund University, Skane University Hospital, Department of Clinical Sciences, Division of Neuroradiology, Lund, Sweden

ⁱ Lund University, Hallands Hospital Halmstad, Department of Anaesthesia and Intensive Care, Halmstad, Sweden

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ABSTRACT

Introduction: A multimodal approach to prognostication of outcome after cardiac arrest (CA) is recommended. Evidence for combinations of methods is low. In this post-hoc analysis we described findings on head computed tomography (CT) after CA. We also examined whether generalised oedema on CT alone or together with the biomarker Neuron-specific enolase (NSE) could predict poor outcome.

Methods: Patients participating in the Target Temperature Management after out-of-hospital-cardiac-arrest-trial underwent CT based on clinical indications. Findings were divided into pre-specified categories according to local radiologists descriptions. Generalised oedema alone and in combination with peak NSE at either 48 h or 72 h was correlated with poor outcome at 6 months follow-up using the Cerebral Performance Category (CPC 3–5).

Results: 356/939 (37.9%) of patients underwent head CT. Initial CT \leq 24 h after CA was normal in 174/218 (79.8%), whilst generalised oedema was diagnosed in 21/218 (9.6%). Between days 1–7, generalised oedema was seen in 65/143 (45.5%), acute/subacute infarction in 27/143 (18.9%) and bleeding in 9/143 (6.3%). Overall, generalised oedema predicted poor outcome with 33.6% sensitivity (95%CI:28.1–39.5) and 98.4% specificity (95%CI:94.3–99.6), whilst peak NSE demonstrated sensitivities of 61.5–64.8% and specificity 95.7% (95%CI:89.5–98.4). The combination of peak NSE $>$ 38 ng/l and generalised oedema on CT predicted poor outcome with 46.0% sensitivity (95%CI:36.5–55.8) with no false positives. NSE was significantly higher in patients with generalised oedema.

Conclusion: In this study, generalised oedema was more common $>$ 24h \leq 7d after CA. The combination of CT and NSE improved sensitivity and specificity compared to CT alone, with no false positives in this limited population.

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Introduction

Brain injury is the main cause of death for patients hospitalised after cardiac arrest (CA) and most die following withdrawal of life sustaining therapy (WLST) due to a prediction of poor neurological prognosis [1]. A multimodal approach to prognostication is recommended, in which the results of a clinical neurological examination is considered together with findings of electrophysiological investigations, serum biomarkers and neuroimaging [2–4]. However, the

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* Corresponding author at: Department of Neurology, Skane University, Hospital, 22185 Lund, Sweden.

E-mail address: marion.moseby@med.lu.se (M. Moseby-Knappe).

evidence for specific combinations of prognostication tools is limited [2–4]. In a large and mainly European survey, head computed tomography (CT) and EEG were the most frequently used methods for prognostication to supplement a clinical neurological examination [5]. CT is widely available and, compared with magnetic resonance imaging, cheaper and easier to perform on ICU patients. CT is often performed upon admission to rule out non-cardiac causes of arrest and contraindications for targeted temperature management (TTM) [5–7].

Within minutes of cerebral ischemia, energy depletion leads to cytotoxic oedema, mainly in the grey matter. During the following days, vasogenic oedema will enhance the swelling [8]. Global hypoxic-ischemic oedema after cardiac arrest may be recognized on a non-contrast enhanced CT as a reduced differentiation between grey and white matter and effacement of the cortical sulci [9]. It is a sign that correlates with poor neurological outcome after CA, but the level of evidence is low [10–12]. In addition, data from long-term follow-up are limited and possible bias regarding selection of patients for CT examinations applies to the majority of studies [6,10,11,13–25]. To standardize image interpretation, various techniques of manual and automated measurements of density in the basal ganglia and cerebrum have been employed to calculate a grey-white-matter ratio that correlates with poor outcome, but there is currently no consensus on method nor cut-off values to use in clinical practise [6,15–22,24].

Neuron-specific enolase (NSE) is a marker of neuronal damage recommended for prognostication after CA [26]. High serum-levels of NSE 48–72 h after CA are predictive of poor neurological outcome [27]. NSE-release after CA correlates to pathologic EEG-patterns and other measures of severe brain injury such as global ischemia on MRI and histopathological examinations [28,29].

The Targeted Temperature Management After Out-of-Hospital Cardiac Arrest Trial (TTM-trial) was an international, multicentre trial randomising patients to 33 °C vs. 36 °C. In this study we described CT findings after CA and investigated whether generalised oedema alone or in combination with peak-NSE predicted poor outcome. Additionally we investigated the relationship of serum NSE levels to cerebral oedema on head CT.

Materials and methods

Patient selection

This was a pre-specified post-hoc analysis of the TTM-trial, registered at clinicaltrials.gov NCT01020916. Ethical committees in each participating country approved the trial protocol. In line with the Helsinki declaration, informed consent was waived or obtained from all patients or relatives according to national legislations [30]. Between November 2010 and January 2013, 36 sites randomised unconscious patients after out-of-hospital-cardiac-arrest to targeted temperature management of either 33 °C or 36 °C. The trial design, statistical analysis plan, primary, secondary and tertiary outcomes have been previously published [31–34].

Computed tomography

The indication of neuroimaging was made at discretion of the responsible physicians and at various time-points after cardiac arrest. The non-contrast CT images were examined by a local radiologist at each study site and the results were entered into the electronic case report form (eCRF) in pre-specified categories; normal, bleeding, infarction, bone fracture, generalised swelling/oedema and other findings specified in writing for each patient. Multiple options were possible. Information regarding timing and findings of the head CT examinations from the database

were systematically extracted and examined. Site investigators were contacted for clarification of incomplete or conflicting data, which were corrected accordingly.

Neuron-specific enolase

29 of 36 TTM sites participated in the biobank. Serum blood samples were collected at 24, 48 and 72 h after return of spontaneous circulation (ROSC) and were pre-analytically processed at the site, aliquoted and frozen to –80 °C before shipment to the Integrated BioBank of Luxembourg for batch-analysis. NSE-analyses were performed 6 months after trial completion using COBAS e601 line with an Electro-Chemi-Luminescent-Immuno-Assay (ECLIA) kit (Roche Diagnostics, Rotkreuz, Switzerland). Haemolysis testing was performed on all samples using the Roche haemolysis index with measurements at 600 and 570 nm. All samples with a positive haemolysis index (≥ 500 mg/l of hemoglobin) were discarded. Detailed information about the data collection and measurement techniques was previously published [27]. NSE-levels at 48 and 72 h have similar predictive values for poor neurological outcome at 6 months after cardiac arrest [27]. To minimize the effect of missing samples at a single time-point, we used the highest available NSE-measurement at 48 or 72 h (peak-NSE) for the present analysis. We used a 48 ng/ml cut-off at 48 h and a 38 ng/ml cut-off at 72 h, accepting 2 false positive patients according to previously published results [27].

Outcomes

Neurological outcome was determined at a face-to-face follow-up approximately 6 months after cardiac arrest using the Cerebral Performance Category Scale (CPC). Good outcome was defined as; good cerebral performance (CPC 1); or moderate cerebral disability (CPC 2). Poor outcome was defined as: severe disability (CPC 3); vegetative state (CPC 4); or brain death (CPC 5).

Prognostication

A physician outside of the ICU team and blinded for treatment allocation made a neurological prognostication for each patient, according to the previously described protocol, resulting in a recommendation to either “continue active care”, “not to escalate care” or to “withdraw life-sustaining-therapy”. Decisions on the level of care were left at the discretion of the responsible physicians.

Statistical analysis

Continuous variables are expressed as median (interquartile range) and categorical variables as number of patients (percentages). Mann–Whitney U and Chi-squared tests were used to compare continuous and categorical variables respectively. Tests are two-sided and p -values < 0.05 were considered statistically significant. The sensitivities and specificities for each variable to predict poor outcome are presented with 95% confidence intervals using Wilson’s method. Analyses were performed using SPSS software version 23. Groups of patients are categorised by timing of CT less than 24; between 24 h and 168 h; and > 168 h after CA. NSE-values were calculated using the available peak value of measurements carried out at either 48; or 72 h after cardiac arrest.

Results

Patient demographics

Of 939 included patients, 357 (37.9%) underwent at least one head CT between CA and ICU-discharge. Among these, 36 (1.0%)

Table 1
Patient demographics.

	All patients	Non-CT	CT	p-value
Number of patients	939 (100)	582 (62)	357 (38)	
Age	65 (56–73)	65 (56–73)	65 (57–73)	0.916
Male	761 (81)	484 (83)	276 (77)	0.330
Location of CA				0.022
Place of residence	500 (53)	315 (54)	184 (52)	
Public place	385 (41)	225 (39)	161 (45)	
Other	53 (6)	41 (7)	12 (3)	
Temperature 33°	473 (50)	298 (51)	174 (49)	0.489
Initial rhythm shockable	752 (80)	487 (84)	257 (72)	<0.001
Time to ROSC (min)	25 (17–39)	25 (16–40)	27 (18–40)	0.198
Poor outcome (CPC 3–5) at 6 months	494 (53)	257 (44)	236 (66)	<0.001

Data are numbers of patients and percentages or medians and interquartile range (IQR). CA: cardiac arrest; ROSC: return of spontaneous circulation; CPC: cerebral performance category; CT: head computed tomography.

Table 2
Distribution of findings on head computed tomography after cardiac arrest.

	≤24h	>24 h ≤ 7 days	>7 days	all
n = Time to CT	218 (55.8) 2 (1–4)	143 (36.5) 77 (53–114)	30 (7.7) 245 (193–348)	391 8 (2–79)
CT findings				
Normal	174 (79.8)	50 (35.0)	15 (50.0)	239 (61.1)
Bleeding	7 (3.2)	9 (6.3)	4 (13.3)	20 (5.1)
Infarction	5 (2.3)	27 (18.9)	4 (13.3)	36 (9.2)
Oedema	21 (9.6)	65 (45.5)	5 (16.7)	91 (23.2)
Bone fracture	4 (1.8)	0 (0)	1 (3.3)	5 (1.3)
Other	34 (15.6)	19 (13.3)	9 (30)	62 (15.8)

Data are given in numbers and percentages for CT findings and in median and IQR for time to CT. CT: computed tomography, Time to CT: hours from cardiac arrest to head CT. n: number of patients, h: hours, Multiple options possible.

patients underwent a second CT for reasons not specifically stated. The baseline characteristics were similar in the CT and the non-CT group regarding age, gender, targeted temperature and time to ROSC (Table 1). The initial rhythm was more often shockable and outcome significantly better in the non-CT group. The frequency of patients undergoing CT varied substantially amongst the individual centres from 6.9% to 83.3% of the patient population.

CT findings

More than half of CT examinations were performed within 24 h after CA (median 2 h). Of these, 79.8% were classified as normal and 9.6% with generalised oedema (Table 2). In CT-examinations performed 24 h–7 d post-arrest, cerebral oedema was diagnosed in 45.5%. Patients performing CT 24 h–7 d after CA more often had a poor neurological outcome compared to patients with CT performed before 24 h (80% versus 60%, ($p < 0.001$)). Of the patients with bleeding on CT, only one initial CT (2 h after CA) was reported with massive subarachnoid haemorrhage (SAH) and was excluded from further analyses. The other reported bleedings were either small traumatic SAH or late CTís with suspected haemorrhagic transformations. The type of bleeding was not specified for 7/20 (35%).

Generalised oedema as a predictor of poor outcome

Within the first 24 h after cardiac arrest, generalised oedema predicted poor outcome with 14.4% sensitivity (95%CI:9.4–21.4) and 97.6% specificity (95%CI:91.8–99.4) (Table 3). Even if early CT did not show oedema, 58% of examined patients still had poor outcome at 6 months.

Generalised oedema on head-CT 24 h–7 d post-arrest demonstrated 56.5% sensitivity (95%CI:47.3–65.3) and 100% specificity (95%CI:87.9–100.0) for predicting poor outcome. The positive pre-

dictive value for patients with generalised cerebral oedema having poor outcome was 90.5% in the first 24 h after CA and increased to 100% at 24 h–7 d. In all, two false positive predictions occurred, both in the early-CT (≤24 h) group and treated by 36 °C targeted temperature. Sensitivity was 37.6% in the 33 °C and 29.5% in the 36 °C group; specificity 100% and 96.7%, respectively.

Among 36 patients undergoing head CT twice, 15 (41.7%) had findings of generalised oedema on the second CT, performed at a median of 77 h after CA (IQR: 41–121 h). Only one of these patient demonstrated signs of generalised oedema on the preceding CT examination, 2 h after CA.

NSE

7 TTM-trial centres did not participate in the biomarker study, resulting in a loss of NSE-samples from 122/939 (13.0%) patients. Peak NSE-level at either 48 or 72 h after CA was available for 70.9% of the overall CT population and 67.5% of the overall non-CT population. 11 samples were excluded due to hemolysis.

Peak NSE was significantly higher in patients with generalised oedema than in patients without generalised oedema ≤24 h; median 178 ng/ml (IQR:22–236) vs. 19 ng/ml (IQR:13–73); ($p = 0.012$) and remained significantly higher 24 h–7 d days post arrest, median 135 ng/ml (IQR: 70–201) vs. 26 ng/ml (IQR: 15–63) ($p < 0.001$) (Fig. 1). There was no significant difference between peak-NSE levels in patients examined with initial head CT ≤24 h, compared to NSE-levels in patients undergoing CT within one week after CA ($p = 0.85$).

Of 91 patients with signs of generalised oedema on CT at any time-point, only 4 survived to 6 months follow-up, 2 in CPC 1 and 2 in CPC 3. The 2 patients in CPC 1 had peak NSE-values of 15 and 21 ng/ml and their CT was carried out at 3 and 10 h after CA, respectively. One patient in CPC 3 had peak-NSE 23 ng/ml and the other 84 ng/ml; these patients underwent late CTís at 159 h and 212 h after CA, respectively. The four survivors with generalised oedema on CT were younger than the average study population (45–58 years old). They all had CPC 1 pre-arrest and a shockable rhythm on the initial ECG. Time to ROSC varied between 23 and 39 min.

Using a cut-off at 38 ng/ml, peak-NSE identified patients with poor outcome in the whole CT-examined population with 64.8% sensitivity (95%CI:57.6–71.5) and 95.7% specificity (95%CI:89.5–98.4). Using a 48 ng/ml cut-off, results were similar with sensitivity 61.5% (95%CI:54.3–68.3) and identical specificity 95.7% (95%CI:89.5–98.4) (Table 3).

Combining head CT and NSE

The combination of head CT and peak-NSE improved sensitivity to predict poor outcome compared to early CT alone (Sensitivities: cut-off 38 ng/ml: 46.0% (95%CI:36.5–55.8), cut-off 48 ng/ml:

Table 3
Prediction of poor outcome after cardiac arrest with generalised oedema on head CT and Peak- Neuron-specific enolase (NSE).

Variable	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	All n	TP n	FP n	TN n	FN n
All CT examinations	33.6 (28.1–39.5)	98.4 (94.3–99.6)	97.8	41.3	392 ^a	89	2	124	176
CT ≤ 24h	14.4 (9.4–21.4)	97.6 (91.8–99.4)	90.5	42.3	218 ^a	19	2	83	113
CT > 24h ≤ 7days	56.5 (47.3–65.3)	100 (87.9–100.0)	100	35.9	143	65	0	28	50
CT > 7 days	27.8 (12.4–50.9)	100 (75.7–100.0)	100	48.0	30	5	0	12	13
Peak-NSE >38 ng/ml	64.8 (57.6–71.5)	95.7 (89.5–98.4)	96.7	58.4	276	118	4	90	64
Peak-NSE >48 ng/ml	61.5 (54.3–68.3)	95.7 (89.5–98.4)	96.6	56.3	276	112	4	90	70
CT + Peak-NSE >38 ng/ml	46.0 (36.5–55.8)	100 (95.6–100.0)	100	61.2	185	46	0	85	54
CT + Peak-NSE >48 ng/ml	45.9 (36.8–55.3)	100 (95.6–100.0)	100	59.0	194	50	0	85	59

Data are given in numbers and percentages. CI: 95% confidence interval. CT: computed tomography, Peak-NSE: maximum Neuron-specific enolase at either 48 h or 72 h reported in CT-subgroup, PPV: positive predictive value; NPV: negative predictive value; n: number of patients; TP: true positive; FP: false positive; TN: true negative; FN: false negative.

^a Missing data outcome for 1 patient. 36 patients underwent two CT examinations and were reported twice. Cut-off values NSE are representing 48 h (48 ng/ml); and 72 h (38 ng/ml); values accepting a 2% false positive ratio according to article published by Stammet et al. [27].

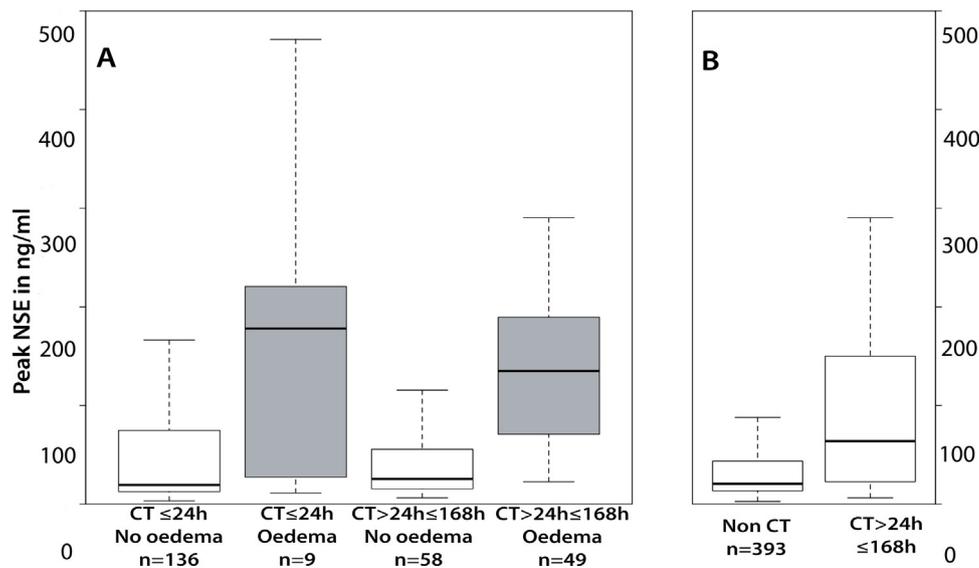


Fig. 1. Serum peak NSE levels after cardiac arrest.

A + B: Peak NSE levels in ng/ml at either 48; or 72 h after cardiac arrest. Data is presented in numbers or median and interquartile range. CT: head computed tomography. NSE: Neuron-specific enolase. Fig. 1A: peak NSE in patients with or without generalised oedema on head CT within 24 h or between days 2–7 post arrest. Fig. 1B: peak NSE levels in patients not undergoing head CT compared to patients undergoing head CT between days 2–7 post arrest.

45.9% (95%CI:36.8–55.8)), and eliminated the few false positives (Specificity 100% (95%CI:95.6–100.0)) (Table 3). Likelihood ratios are presented in the Supplementary Table 1.

Neurological prognostication

Neurological prognostication was performed in 170/357 (47.6%) patients examined with head CT, at a median of 120.0 h after CA (IQR:101–143 h). Reasons for not undergoing prognostication was regaining consciousness in 133/187 (71.1%), death before prognostication in 43/187 (23.0%) and other reasons in 11/187 (5.9%).

63/91 (69.0%) patients with generalised oedema on CT underwent prognostication at median 122 h after CA (IQR: 97–144 h). CT findings were reported as part of the decision in 47/63 (74.6%). The recommendation was to continue active care in 8/63 (12.7%), not to escalate care in 16/63 (25.4%) and to withdraw life-sustaining therapy in 39/63 (61.9%). 20/356 (5.6%) of patients undergoing CT were subsequently classified as brain death including 3/39 (7.7%) patients with WLST recommendation. 8/91 (8.8%) patients with generalised oedema had NSE-levels below the FPR 2 cut-offs at 48 h and 72 h. All of these patients had other findings predicting poor prognosis (early status myoclonus, absent corneal and/or pupillary reflexes, status epilepticus or suppression burst on EEG, absent SSEP

bilaterally) and the decision to withdraw life-sustaining therapy was never based on CT alone in any of these patients.

Discussion

In this large sample we could confirm that findings of generalised oedema on non-contrast enhanced head computed tomography, assessed by a local radiologist, is a reliable predictor of poor outcome after cardiac arrest.

CT is easily available and routinely performed at many centres to rule out non-cardiac causes of arrest. Presence of generalised oedema may be of value to guide treatment decisions and to give early information to relatives about expected prognosis. The sensitivity of generalised oedema on CT performed initially after CA is apparently limited; in our study only 14.4% of patients with a subsequently poor outcome were identified this way. In our cohort, sensitivity appeared to increase from 14.4 to 56.6% when CT was delayed beyond 24 h. This major increase is likely exaggerated by selection bias, indicated by the high NSE-levels among patients with later CT. Thus, if all patients still comatose in the first days after CA had undergone CT, the corresponding sensitivity would probably lie in between that of initial screening with CT (14.4%) and that of patients with CT > 24 h but < 7 days (56.5%).

Theoretically, vasogenic oedema could develop over time, causing an increase in sensitivity when CT is performed at a later time-point. Due to lacking studies performing repeated CT scans in a systematic fashion, this is currently an area of uncertainty. Of the 36 patients with repeated CT scans, 41% demonstrated generalised oedema on a second CT-scan. Only one of these was identified on the preceding scan. Again, we recognise the possibility of further selection as the indication for repeated CTs may be less given a previous pathological finding.

That visible generalised oedema on CT is a very grave sign is evident by the comparatively high levels of NSE obtained in this sub-group of our patients. Although comparisons are limited by methodological differences, the NSE-levels we found among patients with CT-identified oedema were roughly twice those previously reported for patients with extensive lesions on MRI [28] and lack of EEG-reactivity [29], other markers of poor prognosis after cardiac arrest. In our study, the interpretation of CT was left at the local radiologists discretion, representing a pragmatic approach to “real life” patient management. In the two patients classified with generalised oedema on initial head CT, low NSE-values and good outcome, we believe that oedema may have been incorrectly described, again stressing the importance of the recommended multimodal approach to prognostication [2–4]. The potential reversibility of early oedema is still an area of uncertainty, although primary injury due to cytotoxicity is associated with substantial neuronal loss [35].

The added value of the NSE-measurement was to identify the few but highly relevant false positive patients with signs of early generalised oedema on CT but good final outcome. In a previous smaller study, Lee et al. measured grey-white matter ratios and found that the prognostic performance was increased when CT was combined with NSE, supporting our results [36].

In the TTM-trial, CT was not part of prognostication protocol, but our analyses demonstrated that findings were considered when making recommendations on further treatment. It was not the TTM-investigators intention to limit any prognostic information support for necessary decisions on continued or withdrawn intensive care.

Visual evaluation of non-contrast-enhanced brain-CT is one of the most commonly used methods to assist prediction of outcome after CA [5]. It is still uncertain if quantitative assessment of oedema is superior to a radiologist’s estimation. To our knowledge, there are no studies on the interrater variabilities of visual evaluations on CT findings after CA.

In patients with NSE levels below the FPR 2 cut-off described previously [27], our investigations could not show that isolated CT findings motivated WLST. Still, we recognize the apparent risk of a self-fulfilling prophecy whereby generalised oedema may have influenced decisions on level-of-care in this study. NSE-levels reported in the TTM-trial were analysed after follow-up of the last patient, but some centres may have performed local NSE-measurements, whose results might possibly have influenced treatment decisions on some sites.

Strengths and limitations

This CT study in cardiac arrest patients from the TTM trial is the largest of its kind and the first to investigate various aspects of the correlation between NSE in serum, generalised oedema and outcome at 6 months. Due to the extensive documentation in the TTM trial, it contains valuable information on neurological prognostication and withdrawal of life-sustaining therapy.

The study is limited by its retrospective nature and by the fact that CT was not a mandatory examination in the TTM-trial, making selection bias probable. However, many centres routinely performed early CT, and NSE results support the risk of selection

bias being less in the early-CT group, even though the number of patients with oedema in this subgroup was small. There was only a brief protocol to describe CT findings, interrater variability cannot be excluded. The CT equipment and experience of the local radiologists was not collected but likely varied extensively in this multi-centre trial. Collection of CT-images was not part of protocol and considered unfeasible for this study. Therefore, we cannot validate the findings by the local examiners but we still consider that our results are representative for the general usage of CT for prognostication and in particular in combination with an other independent prognostic marker as recommended in guidelines [2–4].

NSE values were missing for a substantial fraction of patients as some centres did not participate in the biomarker study. This loss of data on a centre level is not likely to contribute to selection bias but reduces our ability to draw conclusions, especially in the group with early signs of generalised oedema.

Finally, we recognise the risk of the self-fulfilling prophecy affecting our results on the prognostic performance of head CT since the findings were available for the clinician performing prognostication. NSE was analysed after the trial, even though a small amount of centres might have made their own parallel analyses of biomarkers.

Conclusions

Head CT is an easily available tool that can help identify patients with very severe brain injury early after cardiac arrest. The combination of head CT with serum NSE-levels increased the prognostic performance further providing evidence for multi-modal algorithms. Further studies are needed to determine the optimal timing of head CT after cardiac arrest and whether standardised assessments can be used to increase reliability further.

Conflict of interest statements

M. Moseby-Knappe, I. Dragancea, A. Roncarati, J. Undén, R. Siemund and T. Cronberg declare no conflicts. H. Friberg serves on the scientific advisory board of QuickCool, and has received honoraria for lectures from Natus Inc, and Bard Medical. N. Nielsen has received honoraria from Bard Medical. T. Pellis and J. Horn have received honorarium for lectures from Bard Medical.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2017.06.027>.

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