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Short paper

Brain injury markers in blood predict signs of hypoxic ischaemic encephalopathy on head computed tomography after cardiac arrest

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Abstract

Background/Aim: Signs of hypoxic ischaemic encephalopathy (HIE) on head computed tomography (CT) predicts poor neurological outcome after cardiac arrest. We explore whether levels of brain injury markers in blood could predict the likelihood of HIE on CT.

Methods: Retrospective analysis of CT performed at 24–168 h post cardiac arrest on clinical indication within the Target Temperature Management after out-of-hospital cardiac arrest-trial. Biomarkers prospectively collected at 24- and 48 h post-arrest were analysed for neuron specific enolase (NSE), neurofilament light (NFL), total-tau and glial fibrillary acidic protein (GFAP). HIE was assessed through visual evaluation and quantitative grey-white-matter ratio (GWR) was retrospectively calculated on Swedish subjects with original images available.

Results: In total, 95 patients were included. The performance to predict HIE on CT (performed at IQR 73–116 h) at 48 h was similar for all biomarkers, assessed as area under the receiving operating characteristic curve (AUC) NSE 0.82 (0.71–0.94), NFL 0.79 (0.67–0.91), total-tau 0.84 (0.74–0.95), GFAP 0.79 (0.67–0.90). The predictive performance of biomarker levels at 24 h was AUC 0.72–0.81. At 48 h biomarker levels below Youden Index accurately excluded HIE in 77.3–91.7% (negative predictive value) and levels above Youden Index correctly predicted HIE in 73.3–83.7% (positive predictive value). NSE cut-off at 48 h was 48 ng/ml. Elevated biomarker levels irrespective of timepoint significantly correlated with lower GWR.

Conclusion: Biomarker levels can assess the likelihood of a patient presenting with HIE on CT and could be used to select suitable patients for CT-examination during neurological prognostication in unconscious cardiac arrest patients.

Introduction

Signs of hypoxic ischaemic encephalopathy (HIE) on head computed tomography (CT) or magnetic resonance imaging (MRI) are guideline recommended predictors of poor neurological outcome after cardiac arrest.[1,2] HIE on CT is qualitatively assessed through visual evaluation of generalised oedema and quantitatively calculated from grey-white-matter ratio (GWR).[1] Reduced GWR is a 100% specific predictor of poor neurological outcome but lacks consensual thresholds and standardised methods for interpretation, resulting in varying levels of sensitivity.[1–6] Certain MRI sequences may be more sensitive to acute structural damage than CT, but is more expensive and offers limited possibilities to monitor haemodynamically and respiratory unstable patients during the extended examination.[1] There is

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Table 1 – Demographics of study population.

	Biomarkers 24 h CT 24-168 h		Biomarkers 48 h CT 48-168 h	
	Included (n=94)	Excluded (n=845)	Included (n=75)	Excluded (n=864)
Baseline data				
Age *years*	65.0 (58.0-72.0)	65.0 (56.0-73.0)	65.0 (59.0-71.0)	65.0 (56.0-73.0)
Male	73 (77.7)	688 (81.4)	58 (77.3)	703 (81.4)
Time to ROSC *minutes*	26 (20-43)	25 (17-39)	26 (20-43)	25 (17-39)
Initial shockable	68 (72.3)	661 (78.2)	56 (74.7)	673 (77.9)
GCS-M 1-3 *on day 4*	49/86 (57.0)	179/683 (26.2)	41/73 (56.2)	187/696 (26.9)
Head CT examinations				
Time to scan *hours*	77.5 (52.0-112.0)	3.0 (1.0-10.75)	91.0 (73.0-115.5)	3.0 (1.0-23.0)
Missing Data		615		615
Normal	32 (34.0)	196/263 (74.5)	24 (32.0)	204/282 (72.3)
Signs of HIE	46 (48.9)	32/263 (12.2)	38 (50.7)	40/282 (14.2)
Biomarkers				
NSE *ng/ml*	34.9 (19.6-66.9)	22.4 (14.8-38.6)	68.4 (23.3-130.4)	20.0 (12.7-46.3)
NFL *pg/ml*	1459.6 (209.5-3283.3)	83.2 (28.6-834.8)	3222.6 (670.4-7909.1)	115.7 (36.8-2032.3)
Total-tau *pg/ml*	8.8 (3.9-39.5)	4.2 (1.8-13.0)	28.4 (6.3-118.4)	3.6 (1.5-28.4)
GFAP *pg/ml*	99.7 (47.2-1041.3)	48.3 (22.2-115.3)	123.2 (66.8-2066.2)	52.3 (24.7-139.7)
Neurological outcome at six months				
Good *1-2 CPC*	21 (22.3)	419 (49.6)	15 (20.0)	425 (49.2)
Poor *3-5 CPC*	73 (77.7)	420 (49.7)	60 (80.0)	433 (50.1)

Results presented as median (IQR) for numeric variables and as count of numbers (%) for ordinal variables. ROSC = Return of spontaneous circulation. GCS-M = Glasgow Coma Scale Motor on day 4 (72–96 h post-arrest), 1–3 = no reaction to pain stimulus, abnormal extension or flexion, hence eligible for prognostication of neurological outcome according to current guidelines.[1] HIE = Hypoxic-ischaemic encephalopathy. CPC = Cerebral Performance Categories (1–2 = good outcome, no or moderate neurological deficit, 3–5 = poor outcome, severe deficit, unresponsive wakefulness or death) at 6 months.[21] The total amount of included patients was 95, one patient had available biomarker levels at 48 h only.

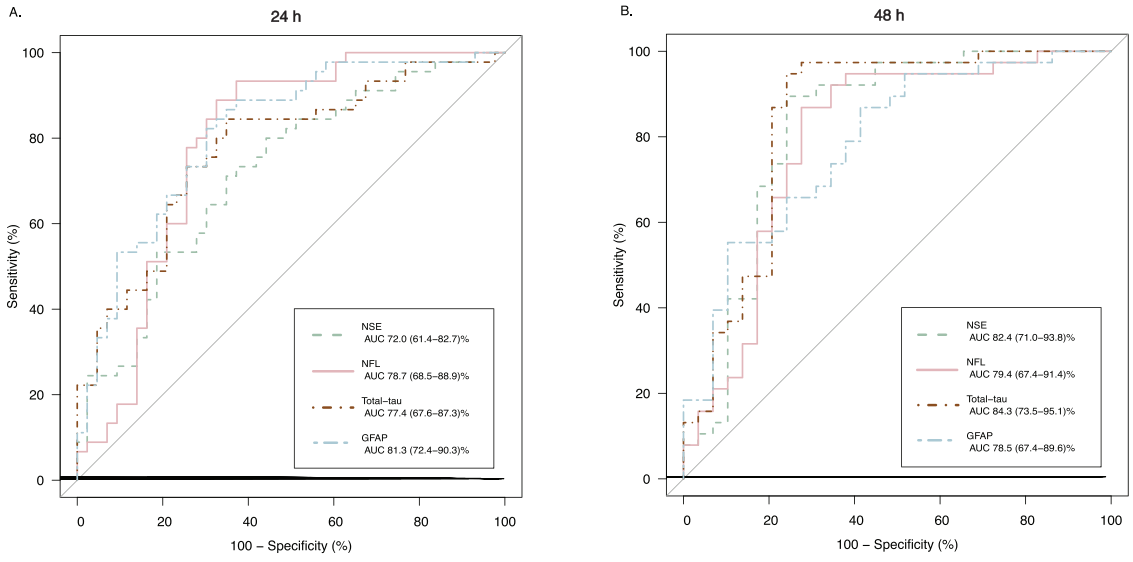

Fig. 1 – A-B. Performance of biomarker levels to predict signs of HIE. Significance level and 95% CI calculated by bootstrap procedure, (N = 2000 iterations). A. Biomarker levels at 24 h and CT scans performed at 24–168 h post arrest, N = 88. B. Biomarker levels at 48 h and CT scans performed at 48–168 h post arrest, N = 67.

currently no method to guide the choice of suitable neuroimaging modality.

Elevated levels of neuron specific enolase (NSE) ≥60 ng/ml at 48 or 72 h (h) post-arrest is another predictor of poor neurological outcome and has previously been associated with HIE on CT.[1,7] The novel brain injury markers neurofilament light (NFL) and total-tau have shown superior prognostic accuracy to NSE at 24–72 h.[2,8–10] Astrocytic glial fibrillary acidic protein (GFAP) is an early marker of glial injury and increased astrocytic activity.[1,11,12] The earliest guideline recommended timepoint for NSE evaluation is 48 h, which is a

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timepoint where all four biomarkers mentioned above have demonstrated reasonable prognostic accuracies.[1,8,9,12] NFL has additionally demonstrated excellent predictive performance for neurological outcome already at 24 h.[13] CT performed from biomarker sampling and up to 7 days after cardiac arrest were considered eligible for prognostication.[1]

The aim of this study was to describe the association between brain injury marker levels in blood and signs of HIE on CT. We examined whether biomarker levels at 24- and 48 h could be used as an individualised decision aid for determining whether CT is likely sufficient for HIE diagnosis. This could reduce the number of neuroradiological examinations necessary to predict neurological outcome in unconscious patients after cardiac arrest and enable wisely spent resources in post-arrest care.

Materials and methods

Study population

Retrospective analysis of the prospective Target Temperature Management after out-of-hospital cardiac arrest (TTM)-trial, which included adult unconscious patients with presumed cardiac cause of arrest.[7,14]

Biomarkers

Brain injury markers in blood prospectively collected at 24- and 48 h after randomisation were analysed after trial completion.[14,15] NSE concentrations were measured using COBAS e601 line with electrochemiluminescence immunoassay (ECLIA) kit (Roche Diagnostics).[15] All samples were tested for haemolysis and discarded if positive, as previously described.[15] NFL and total-tau concentrations were measured using an ultrasensitive single molecule array (Simoa™) method (Quanterix Billerica, MA), with a homebrew kit and a human total-tau kit respectively.[8,9,16,17] GFAP concentrations were measured using sandwich enzyme-linked immunosorbent assay (ELISA) (Banyan Biomarkers).[18]

Neuroimaging

CT was performed according to clinical indication. Primary outcome was signs of HIE on CT, qualitatively assessed by on-site radiologists through visual evaluation of generalised oedema as previously described.[14] These results were available during clinical decision-making. Quantitative GWR was retrospectively evaluated on original scan images from Swedish sites by a radiology resident with approximately-3 years of experience (ML), blinded to clinical data.[19] 16 regions of interest (ROI) of approximately 0.1 cm^2 (60 pixels) were used to calculate the GWR as previously described by Metter et al.[20] For scatter plot illustrations, neurological outcome at 6 months was dichotomized into good (Cerebral Performance Category scale (CPC) 1–2) or poor (CPC 3–5).[21]

Statistical analysis

The predictive capacity of biomarker levels at 24- and 48 h was assessed for CT examinations performed at 24–168 and 48–168 h, respectively. The earliest timepoint was chosen to explore the predictive capacity of early decision-making and the latter was determined by the earliest guideline recommended timepoint for NSE analysis in neurological prognostication after cardiac arrest.[1] Kruskal Wallis statistical test was used for comparing binary outcome (presence/absence of HIE). Spearman's rank-order correlation test was

Table 2 – Youden calculated cut-offs at 24- and 48 h. Results are presented with 95% CI. PPV = Positive Predictive Value; percentage of correctly confirmed hypoxic-ischaemic encephalopathy (HIE) in patients with elevated biomarker levels. NPV = Negative Predictive Value; percentage of correctly excluded HIE in patients with low biomarker levels. Sensitivity: percentage of all patients with signs of HIE that had biomarker levels elevated beyond this cut-off. Specificity: percentages of all patients without HIE that had biomarker levels below this cut-off. TP = True Positive, elevated biomarkers and signs of HIE on CT. FP = False Positive; elevated biomarker levels without signs of HIE. TN = True Negative, low biomarkers and no signs of HIE. FN = False Negative; low biomarker levels and signs of HIE on CT.

	Biomarkers	Optimal threshold	PPV	NPV	Sensitivity	Specificity	TP	FP	TN	FN
24 h	NSE ng/ml	32.1	68.1 (53.8-79.6) %	68.3 (53.0-80.4) %	71.1 (56.6-82.3) %	65.1 (50.2-77.6) %	32	15	28	13
	NFL pg/ml	720.0	74.1 (61.1-83.99 %	85.3 (69.9-93.6) %	88.9 (76.5-95.2) %	67.4 (52.5-79.5) %	40	14	29	5
	Total-tau pg/ml	6.2	71.7 (58.4-82.0) %	80.0 (64.1-90.0) %	84.4 (71.2-92.3) %	65.1 (50.2-77.6) %	38	15	28	7
	GFAP pg/ml	82.0	74.0 (60.5-84.1) %	78.9 (63.7-88.9) %	82.2 (68.7-90.7) %	69.8 (54.9-81.4) %	37	13	30	8
48 h	NSE ng/ml	48.3	82.9 (68.7-91.5) %	84.6 (66.5-93.9) %	89.5 (75.9-95.8) %	75.9 (57.9-87.8) %	34	7	22	4
	NFL pg/ml	2548.6	80.5 (66.0-89.8) %	80.8 (62.1-91.5) %	86.8 (72.7-94.3) %	72.4 (54.3-85.3) %	33	8	21	5
	Total-tau pg/ml	17.4	83.7 (70.0-91.9) %	91.7 (74.2-97.7) %	94.7 (82.7-98.5) %	75.8 (57.9-87.8) %	36	7	22	2
	GFAP pg/ml	95.8	73.3 (59.0-84.0) %	77.3 (56.6-89.9) %	86.8 (72.7-94.3) %	58.6 (40.7-74.5) %	33	12	17	5
ESICM guideline[1]	NSE ng/ml 48 h	60	78.9 (65.8-90.5) %	75.9 (55.6-85.8) %	81.1 (63.7-88.9) %	73.3 (57.9-87.8) %	30	7	22	8

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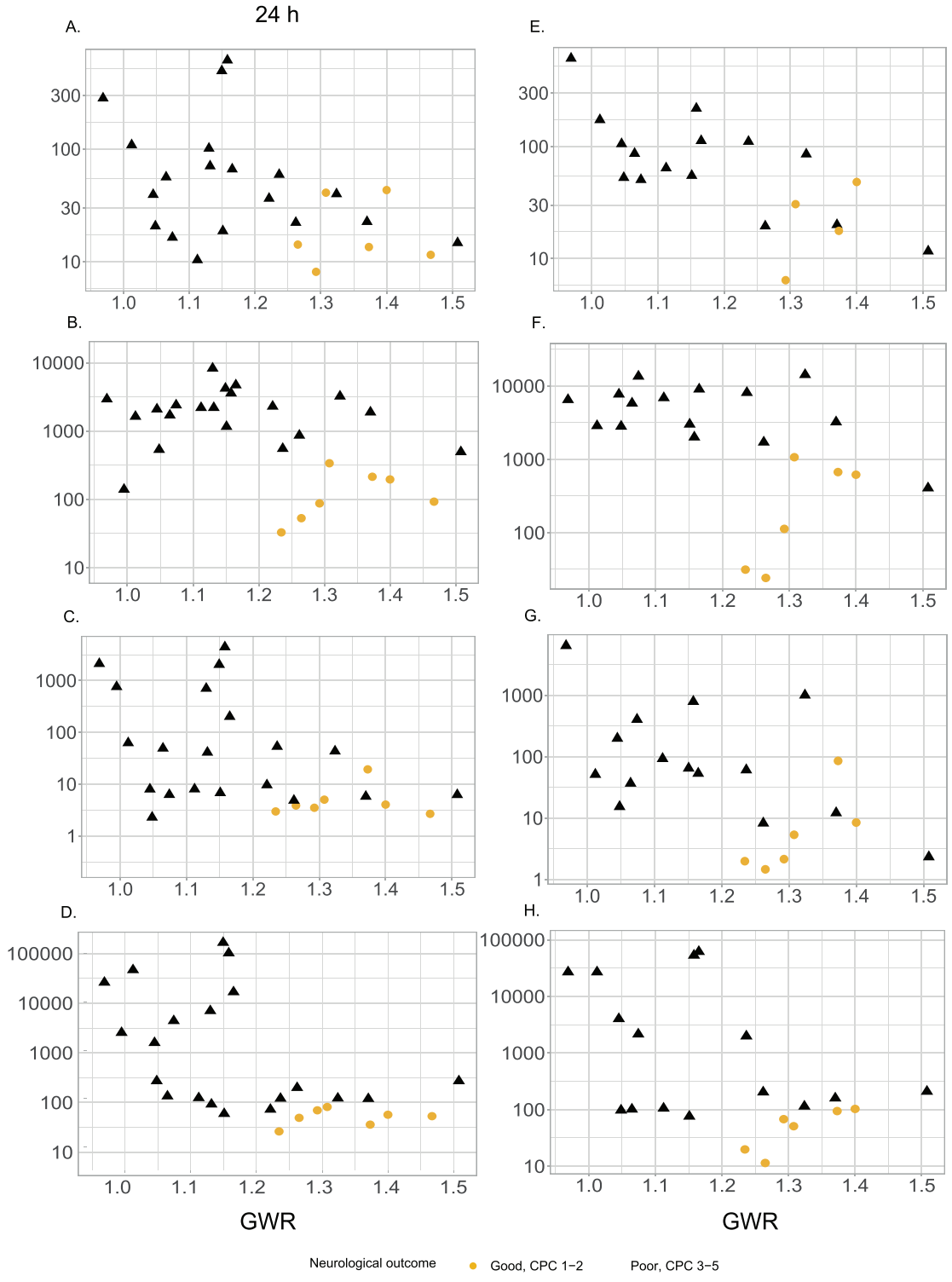

Fig. 2 – Correlation of biomarker levels and quantitative GWR. Scatterplot separated by neurological outcome at 6 months after cardiac arrest; (yellow circles; good outcome, CPC 1–2, black triangles; poor outcome, CPC 3–5).[21] GWR = Grey-White-Matter Ratio, score closer to 1 indicates pathological extinction of normal attenuation difference. A-D, biomarkers 24 h, CT 24–168 h: $N_{NSE} = 25$, $N_{NFL} = N_{Total\text{-}Tau} = N_{GFAP} = 27$. Spearman's rank-order correlation test: NSE $q_{24h} = -0.42$ p = 0.04, NFL $q_{24h} = -0.40$ p-value = 0.04, Total-tau $q_{24h} = -0.49$ p-value = 0.010, GFAP $q_{24h} = -0.62$ p-value < 0.001. E-H, biomarkers at 48 h, CT 48–168 h: $N_{NSE} = 19$, $N_{NFL} = N_{GFAP} = N_{Total\text{-}Tau} = 21$. Spearman's rank-order correlation test: NSE $q_{48h} = -0.69$ p = 0.001, NFL $q_{48h} = -0.44$ p-value = 0.04, Total-tau $q_{48h} = -0.45$ p-value = 0.04, GFAP $q_{48h} = -0.37$ p-value > 0.05.

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used for continuous outcome (GWR). The performance to predict HIE on CT was evaluated by area under the receiving operating characteristic curve (AUC).[22] Significance levels and 95% confidence intervals were calculated through bootstrap procedure (N = 2000 iterations). Biomarker cut-off levels to predict HIE were assessed by Youden index, for optimal sensitivity and specificity. Cut-offs were evaluated by positive predictive value (PPV; percentage of correctly confirmed HIE in patients with elevated biomarker levels) and negative predictive value (NPV; percentage of correctly excluded HIE in patients with low biomarker levels). To improve the readability of graphic illustrations the axes of the biomarker levels were transformed by log10. Scatter plots separated by neurological outcome were used to illustrate individual patients.

P-values ≤ 0.05 were considered statistically significant. All statistical analyses were performed in R version 4.1.2.

Results

In total, 95 patients had available biomarker levels at 24 or 48 h and available CT scan results at 24–168 h, of which 27 patients from Swedish sites had available GWR measurements (Table 1, Fig. S1, Fig S2). All biomarker levels were significantly higher in patients with HIE on CT as compared to patients without HIE, $p < 0.001$ (Fig. S3, Fig. S4, Table S2, Table S3).

Predictive performance

The performance of biomarkers at 24 h to predict HIE on CT (performed at IQR: 52.0–112.0 h) was similar for all biomarkers AUC NSE 0.72 (0.61–0.83), NFL 0.79 (0.69–0.89), total-tau 0.77 (0.68–0.87), GFAP 0.81 (0.73–0.98) (Fig. 1A). The performance at 48 h and CT performed at IQR: 73–116 h was also without significant difference; AUC NSE 0.82 (0.71–0.94), NFL 0.79 (0.67–0.91), total-tau 0.84 (0.74–0.95), GFAP 0.79 (0.67–0.90) (Fig. 1B).

Optimal cut-offs for prediction

Youden Index derived cut-offs for predicting presence or absence of HIE at 48 h were: NSE 48 ng/ml, NFL 2549 pg/ml, total-tau 17 pg/ml and GFAP 96 pg/ml (Table 2). Patients with biomarker levels below cut-offs had very low likelihood of HIE on CT (NPV 77.3–91.7%). Patients with biomarker levels elevated beyond cut-offs had high likelihood of HIE on CT (PPV 73.3–83.7%). Cut-off levels at 24 h had lower predictive accuracy for NSE and total-tau whereas NFL and GFAP had similar predictive performance as compared to 48 h. A sensitivity analysis on patients still unconscious at day 4 was performed with similar results (Table S1).

GWR

Elevated biomarker levels at 24 h significantly correlated with reduced GWR (ρ_{24} h = *negative* 0.40–0.62), $p < 0.05$. At 48 h elevated NSE, NFL and total-tau significantly correlated with reduced GWR (ρ_{48h} = *negative* 0.44–0.69), $p < 0.05$ (Fig. 2). GFAP presented with larger spread in biomarker levels, likely affecting the correlation coefficient and significance level.

Discussion

In this retrospective analysis we present results suggesting that biomarker levels in blood can be used to predict signs of HIE on CT, a highly specific predictor of poor outcome after cardiac arrest. By using biomarker levels as an individualised decision aid to select suitable neuroimaging modality for adequate neurological prognostication, repeated examinations may be avoided – which could save resources and avoid additional risks for patients.

We explored predictive performances of biomarkers at 24- and 48 h. According to international guidelines CT performed prior to 48 h is also of prognostic relevance, although its sensitivity in prediction has been reported to vary based on timing.[1,5,19,23] By using biomarker levels at 24 h post-arrest more patients could be individually assigned to suitable neuroimaging modality with lower yet acceptable accuracy.

We found that the optimal cut-off for NSE to predict signs of HIE on CT at 48 h was 48 ng/ml. Patients with biomarker levels $\geq$48 ng/ml were most often sufficiently examined with CT. Patients with NSE levels <48 ng/ml had very low likelihood of HIE on CT and we therefore suggest MRI to be considered for these patients to adequately map the extent of structural damage. This cut-off may reasonably apply on first examinations as well as for repeated neuroimaging on patients with early normal CT and delayed awakening.[5,7,23] NFL, total-tau and GFAP are not yet routinely available, which limits their clinical use. As their availability increase, their concentrations could also be used to guide decisions on neuroimaging modality. The applicability of this decision aid is determined by the accessibility to prompt biomarker analysis.

The correlation of elevated biomarker levels and reduced GWR aligns with the results of qualitatively measured HIE on CT. Due to the lack of clinically established cut-off values for GWR and considering the small sample size, we decided to not perform any further calculations on prognostic accuracy.[1,4]

Strengths of this study include the prospective sampling and retrospective analysis of biomarker levels to avoid bias caused by having the analysis results upon clinical decision making as well as the blinded GWR assessements.[8,9,12,14,15] Limitations include selection of poor outcome patients, limited sample size, known interrater and inter-scanner variability and lack of standardised approach for GWR-interpretation.[1,4,5,19] Analysis of novel biomarkers were performed with research grade assays.[14]

Conclusion

Biomarker levels can be used to predict the likelihood of HIE on CT and may clinically be used to select suitable neuroimaging modality in unconscious patients after cardiac arrest. Patients with elevated biomarker levels often present with signs of HIE on CT. For patients with low biomarker levels, the likelihood of HIE on CT is very low and other guideline recommended tools for prognostication may instead be considered.

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Role of the Funder/Sponsor

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CRediT authorship contribution statement

Alice Lagebrant: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – original draft, Visualization. **Margareta Lang:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft. **Niklas Nielsen:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Supervision, Project administration, Funding acquisition. **Kaj Blennow:** Investigation, Formal analysis, Resources, Writing – review & editing. **Josef Dankiewicz:** Investigation, Resources, Writing – review & editing. **Hans Friberg:** Investigation, Resources, Writing – review & editing. **Christian Hassager:** Investigation, Resources, Writing – review & editing. **Janneke Horn:** Investigation, Resources, Writing – review & editing. **Jesper Kjaergaard:** Investigation, Resources, Writing – review & editing. **Mikael A. Kuiper:** Investigation, Resources, Writing – review & editing. **Niklas Mattsson-Carlgren:** Investigation, Resources, Writing – review & editing. **Tommaso Pellis:** Investigation, Resources, Writing – review & editing. **Christian Rylander:** Investigation, Resources, Writing – review & editing. **Roger Sigmund:** Investigation, Resources, Writing – review & editing. **Pascal Stammet:** Investigation, Resources, Writing – review & editing. **Johan Undén:** Investigation, Resources, Writing – review & editing. **Henrik Zetterberg:** Investigation, Formal analysis, Resources, Writing – review & editing. **Matt P. Wise:** Investigation, Resources, Writing – review & editing. **Tobias Cronberg:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Supervision, Project administration, Funding acquisition. **Marion Moseby-Knappe:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Supervision, Project administration, Funding acquisition.

Conflicts of interest

KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Ono Pharma, Pharmatrophix, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, reMYND, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

No other conflicts of interest were reported.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2022.12.006.

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