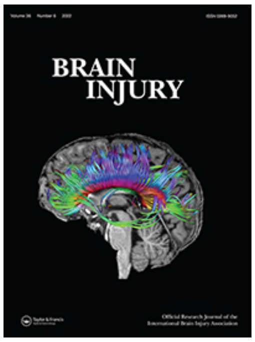

Brain Injury

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ibij20

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To cite this article: Erik Blennow Nordström, Gisela Lilja, Susann Ullén, Kaj Blennow, Hans Friberg, Christian Hassager, Jesper Kjærgaard, Niklas Mattsson-Carlgren, Marion Moseby-Knappe, Niklas Nielsen, Susanna Vestberg, Henrik Zetterberg & Tobias Cronberg (2022) Serum neurofilament light levels are correlated to long-term neurocognitive outcome measures after cardiac arrest, Brain Injury, 36:6, 800-809, DOI: 10.1080/02699052.2022.2048693

To link to this article: https://doi.org/10.1080/02699052.2022.2048693

Published online: 05 Mar 2022.

BRAIN INJURY
2022, VOL. 36, NO. 6, 800–809
https://doi.org/10.1080/02699052.2022.2048693

Serum neurofilament light levels are correlated to long-term neurocognitive outcome measures after cardiac arrest

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ABSTRACT

Objective: To explore associations between four methods assessing long-term neurocognitive outcome after out-of-hospital cardiac arrest and early hypoxic-ischemic neuronal brain injury assessed by the biomarker serum neurofilament light (NFL), and to compare the agreement for the outcome methods.

Methods: An explorative post-hoc study was conducted on survivor data from the international Target Temperature Management after Out-of-hospital Cardiac Arrest trial, investigating serum NFL sampled 48/72-hours post-arrest and neurocognitive outcome 6 months post-arrest.

Results: Among the long-term surviving participants ($N = 457$), serum NFL ($n = 384$) was associated to all outcome instruments, also when controlling for demographic and cardiovascular risk factors. Associations between NFL and the patient-reported Two Simple Questions (TSQ) were however attenuated when adjusting for vitality and mental health. NFL predicted results on the outcome instruments to varying degrees, with an excellent area under the curve for the clinician-report Cerebral Performance Category (CPC 1–2: 0.90). Most participants were classified as CPC 1 (79%). Outcome instrument correlations ranged from small (Mini-Mental State Examination [MMSE]–TSQ) to strong (CPC–MMSE).

Conclusions: The clinician-reported CPC was mostly related to hypoxic-ischemic brain injury, but with a ceiling effect. These results may be useful when selecting methods and instruments for clinical follow-up models.

ARTICLE HISTORY
Received 25 April 2021
Revised 27 December 2021
Accepted 27 February 2022

KEYWORDS
Hypoxic-ischemic encephalopathy; heart arrest; cognitive impairment; biomarker; cardiovascular disease

Introduction

Post-cardiac arrest guidelines recommend that all individuals that survive a cardiac arrest should be offered a follow-up that includes screening for neurocognitive impairments (1). This screening could be used to indicate need of a comprehensive neuropsychological evaluation or rehabilitation interventions to improve quality of life (2). Outcome can be assessed from four methods or perspectives as recommended by the US Food and Drug Administration; through clinician-reports, performance-based measures, patient-reports, and observer-reports (3), which may provide complimentary information. To which extent these outcome methods represent the same construct, e.g., brain injury following out-of-hospital cardiac arrest (OHCA), has not been systematically investigated.

Biomarkers may be used as surrogate markers of brain injury after cardiac arrest (4,5). Neurofilament proteins are markers for neuroaxonal injury (6). Increased levels of neurofilament light chain (NFL) have been found in cerebrospinal fluid and serum or plasma in several neurologic disorders including traumatic brain injury, neurodegenerative diseases, and inflammatory diseases (7). Recently, NFL in blood has emerged as a stronger predictor of poor neurological outcome than other candidate biochemical markers after OHCA (8,9). Still, the association between NFL and neurocognitive impairment after cardiac arrest has not been evaluated.

There are a variety of issues when analyzing possible neurocognitive impairment. Several instruments exist per outcome method and only instruments exhibiting sufficient psychometric properties should be used. Additionally, patient-reported cognitive complaints are often overreported in comparison to objective neurocognitive impairment measured by performance-based tests (10). This skewness could be due to impaired insight, fatigue, or emotional problems such as anxiety, depression, and post-traumatic stress disorder rather than objective neurocognitive

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impairment (11). Furthermore, OHCA mostly occurs in older adults who may have neurodegenerative diseases and/or cardiovascular risk factors, including diabetes mellitus and hypertension (12). These comorbidities are associated with cognitive decline (13,14). A growing number of studies have described neurocognitive deficits following OHCA (15–18). A previous study from our group however reported that neurocognitive impairment was common in both individuals post-OHCA and a matched cohort of subjects who had not suffered OHCA but ST-segment-elevation myocardial infarction (19). These results indicate that vascular comorbidities pre-arrest may be an important factor for neurocognitive performance after OHCA.

The primary aim of this study was to explore the association between early hypoxic-ischemic brain injury as measured by serum NFL and four different outcome methods (clinician-reported, performance-based, patient-reported, observer-reported) in a cohort of individuals post-OHCA. The second aim was to explore the associations between the four outcome methods.

Methods and materials

Participants

We utilized data from the large multi-center Target Temperature Management 33 °C versus 36 °C after out-of-hospital cardiac arrest (TTM) trial (20), ClinicalTrials.gov unique identifier NCT01946932. Within the trial, unconscious patients ≥ 18 years of age with OHCA of a presumed cardiac cause were randomized at hospital arrival to targeted temperature management at 33 °C or 36 °C. The trial found no differences in survival or long-term outcome between the two temperature groups (20,21). This post-hoc study was conducted exclusively on long-term surviving participants from the TTM-trial and combined patients from both temperature groups.

Procedure

Cardiovascular background data were collected on all patients at hospital admission. Serum was sampled at 48 and 72 hours after return of spontaneous circulation (ROSC), aliquoted, and frozen to −80 °C and stored at the Integrated BioBank of Luxembourg (22). After trial completion, NFL concentrations were measured at the neurochemistry laboratory in Mölndal, Sweden, using a homebrew kit on the Simoa HD-1 Analyzer (Quanterix) as previously described (8). NFL data was used for the peak levels, i.e., the highest value at 48 or 72 hours.

Structured face-to-face outcome evaluation was performed at 180 ± 14 days after OHCA where neurocognitive outcome was assessed by four different methods (21). Long-term surviving participants in the TTM-trial completed performance-based and patient-reported measures. Informants, defined as relatives or close friends, completed an observer-report measure. An outcome assessor such as a study nurse, occupational therapist, psychologist or physician, completed clinician-reported measures. Whenever necessary, the evaluation was performed by telephone. The outcome assessor was blinded for the targeted temperature management allocation and biomarkers results.

The TTM-trial was registered as required by legislation and all participating centers had formal ethical approval for the trial. Written informed consent was obtained before the outcome session. The trial was performed from June 2011 to September 2013.

Instruments

As our clinician-reported measure, we used the Cerebral Performance Category (CPC) (23) assessing functional outcome, ranging from 1 (good cerebral performance) to 5 (death). This ordinal scale can be dichotomized into good outcome (CPC 1–2) and poor outcome (CPC 3–5). We have mainly dichotomized good outcome as CPC 1 to increase sensitivity in this study, and only surviving participants were included (CPC 1–4). The outcome assessors were encouraged to include results from other methods, e.g., the performance-based and observer-reported measures in their CPC assessment. No reliability information has been reported for the CPC in its' original form and the construct validity is unclear regarding the ability to measure functioning and health-related quality of life (HRQoL) (24,25). This instrument is however still the most used outcome measure after cardiac arrest.

The performance-based measure utilized in this outcome model was the Mini-Mental State Examination (MMSE) (26), an 11-item screening on global cognitive impairment assessing cognitive domains such as orientation, memory, attention, language, and visuospatial ability. The MMSE scores ranges from 0 to 30 and lower scores indicate greater cognitive impairment. For this study, we only used MMSE results from face-to-face administration. The cutoff level recommended for mild cognitive impairment is < 27, with a level of < 21 classifying moderate-severe impairment (26). The widely used instrument has reasonable diagnostic validity to identify major neurocognitive disorder in a specialist setting, but it exhibits floor and ceiling effects in advanced and very mild neurocognitive disorders, respectively (27). The internal consistency and test–retest reliability has been judged as satisfactory, test performance can however be affected by age, education, cultural background, and emotional problems (28).

As our patient-reported outcome measure, we used question two from the Two Simple Questions (TSQ) (29): "Do you feel that you have made a complete mental recovery after your heart arrest?" (yes/no). If needed, participants were instructed to use their own subjective interpretation of the term "mental recovery." When using both questions, the instrument exhibits acceptable test–retest reliability after stroke (30). Evidence on psychometric properties of the TSQ is limited for use after cardiac arrest; one small study has found acceptable construct validity with significant correlations to measures of cognition and HRQoL, however noting that the impact of emotional problems is uncertain (29).

The observer-report Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest (IQCODE-CA) (31,32) is a 26-item screening questionnaire on decline in everyday neurocognitive function and compares current and pre-arrest neurocognitive function. For this study, we used the index/total score, in which items are summed and divided by the number of completed items, ranging from 1 to 5. Higher scores represent greater cognitive problems. Based on the TTM-trial cohort, an index score of > 3.04 has been suggested to indicate cognitive problems, while > 3.31 previously has been suggested to indicate major neurocognitive disorder (31,32). The original IQCODE has acceptable validity and reliability as a screening for major neurocognitive disorder (31). Our group has previously found that the IQCODE-CA exhibits acceptable internal consistency with small–moderate correlations to both measures of cognition and emotional problems (32).

Statistical analysis

We used Spearman correlations when comparing the association of the continuous full-scale outcome instruments (CPC, MMSE, TSQ, IQCODE-CA) to peak serum NFL. Correlations were reported in accordance with Cohen's guidelines; 0.1–0.29 = Small; 0.3–0.49 = Moderate; > 0.5 = Large (33). We then computed regression models to control for potential covariates, all with NFL as predictor. For the CPC, we performed two logistic regressions, using different definitions of good outcome (CPC 1 and CPC 1–2). Due to ceiling effects on the MMSE and IQCODE-CA, ordinal regressions with several MMSE and IQCODE-CA categories (MMSE 0–20, 21–26, 27–30; IQCODE-CA 0–3.04, 3.05–3.31, 3.32–5) were performed instead. Cut-points were based on earlier studies (26,31,32). One logistic regression was computed for the TSQ. We used an unadjusted regression model, and a second model adjusted for age as NFL concentrations may increase with aging (34). A third regression model was used to examine to which extent demographic factors and comorbidities could explain the outcome scores. This third model was adjusted for demographic factors (sex: male/female; age: continuous variable; level of education: ≤ 12/ > 12 years) and pre-arrest cardiovascular risk factors: diabetes, hypertension, and a summed score of pre-arrest acute myocardial infarction (MI), ischemic heart disease (IHD), and/or coronary artery bypass grafting (CABG) to correct for potential vascular cognitive decline before arrest. Also included in the third model were norm-based scores of the HRQoL domains Vitality and Mental health from the patient-reported outcome measure Short Form 36-Item Health Survey version 2® (SF-36v2®) (35), computed with the Quality Metric Health Outcome™ Scoring Software 4.5. NFL data were $\log_{10}$-transformed in all regressions to reduce skewness.

To compare the degree of predictability on NFL and the respective outcome instruments, we used dichotomized scales to calculate the diagnostic accuracies with receiver-operating characteristic (ROC) plots. Here we examined the area under the curve (AUC) including a 95% confidence interval (CI), with NFL as the independent variable. Dichotomized scores considered as good outcome and representing no–mild brain injury were CPC 1, MMSE ≥ 27, TSQ question two "yes," and IQCODE-CA ≤ 3.04. Additionally, we computed ROC plots for alternate definitions of good outcome. These dichotomized scores, representing no–moderate brain injury, were CPC 1–2, MMSE > 20, TSQ question two "yes," and IQCODE-CA < 3.32.

Next, we tested associations between the continuous outcome instruments using Spearman correlations. As outcome data were on different scales, we additionally dichotomized each instrument with good outcome corresponding with no–mild brain injury, and calculated unweighted Cohen's kappa and percent agreement to investigate the strength of agreement between the instruments. Kappa values were interpreted according to Landis and Koch; < 0 = Poor; 0–0.2 = Slight; 0.21–0.4 = Fair; 0.41–0.6 = Moderate; 0.61–0.8 = Substantial; 0.81–1 = Almost perfect (36).

Statistical significance was set at 2-tailed $p < 0.05$. Statistical analyses were performed using R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics 26.0 (IBM Corp, Armonk, NY, USA).

Results

Participants

At 180 days, 457/486 (94%) of eligible long-term surviving participants had outcome data on CPC and at least one of the other instruments and were included in the study (Figure 1 and Table 1). MMSE data on 30/486 (6%) participants were lost due to telephone follow-up. The fraction of participants with CPC 3–4 did not differ significantly between the 486 and 457 cohorts ($p = 0.23$; Fisher's exact test). The characteristics of the 457 participants are presented in Table 1. The median age at time of cardiac arrest was 62 years (Q_1–Q_3: 53–69) with a median time from cardiac arrest to ROSC of 20 minutes (Q_1–Q_3: 15–30).

Three hundred and eighty-four of the 457 (79%) included participants had NFL analyzed at least once. Peak serum NFL levels were added to the cohort of 457 participants (Figure 1).

Serum NFL associations to the outcome instruments

Serum NFL had a small to moderate association to the continuous outcome instruments, being least associated with the TSQ and most with the CPC (Table 2).

NFL levels were significant in relation to each of the outcome instruments in the unadjusted regression analyses (Table 3). In the age-adjusted model, NFL levels were still significant, with older participants having poorer MMSE and TSQ results, as well as worse outcome on the CPC. In the demographics- and risk factor-adjusted model, older participants had worse IQCODE-CA results. Participants with > 12 years of education performed better on the MMSE than those with less education. Occurrence of previous acute MI, IHD, and/or CABG was associated with worse MMSE results. Lower vitality scores were associated with poorer CPC and IQCODE-CA results, while lower mental health scores were associated with worse MMSE, TSQ, and IQCODE-CA results. When adjusting for vitality and mental health, the relationship between NFL and TSQ was no longer statistically significant. NFL levels were significant in relation to the remaining outcome instruments. Associations to other demographic and cardiovascular risk factors were non-significant.

ROC curves with AUCs for serum NFL to predict results on the dichotomized outcome instruments representing no–mild brain injury in long-term surviving participants are reproduced in Figure 2A. The AUCs ranged from failed on the TSQ: 0.59, 95% CI [0.53–0.65], to fair on CPC 1: 0.78, 95% CI [0.71–0.85]. NFL was overall a stronger predictor of the

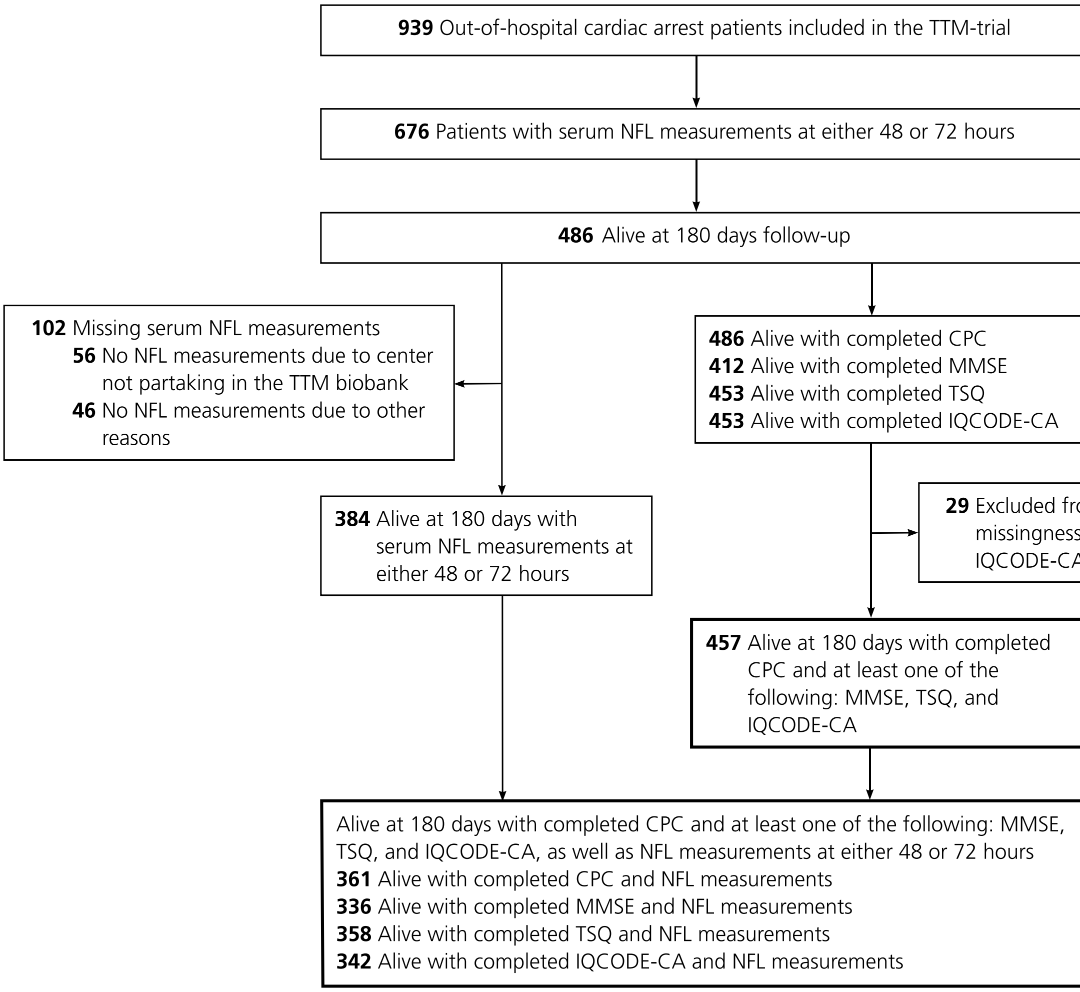

Figure 1. Flowchart of study inclusion. TTM-trial, Target temperature management 33 °C versus 36 °C after out-of-hospital cardiac arrest trial; NFL, neurofilament light chain; CPC, Cerebral Performance Category; MMSE, Mini-Mental State Examination; TSQ, Two Simple Questions; IQCODE-CA, Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest.

Table 1. Demographic and clinical characteristics for the study population (*N* = 457).

	n (%)	Missing, *n* (%)
Male	385 (84)	1 (0)
Education less than 12 years	175 (56)	144 (32)
Comorbidities		
Previous arterial hypertension	162 (36)	2 (0)
Previous diabetes mellitus	56 (12)	3 (1)
Previous ischemic heart disease, acute myocardial infarction, and/or coronary artery bypass grafting	123 (27)	0 (0)
Prehospital variables		
Location of cardiac arrest at home	206 (45)	1 (0)
Bystander witnessed arrest	422 (93)	1 (0)
Bystander CPR	358 (79)	1 (0)
Bystander defibrillation	54 (12)	1 (0)
First monitored rhythm shockable	426 (93)	1 (0)

CPR, cardiopulmonary resuscitation.

alternate, more permissive dichotomizations representing no–moderate brain injury in Figure 2B, with an excellent CPC 1–2 AUC: 0.90, 95% CI [0.83–0.98].

Internal associations between the outcome instruments

Scores from participants on the four long-term outcome instruments are found in Table 4. The instrument that indicated most problems was the observer-reported IQCODE-CA, where 52% of the participants were reported to have some cognitive problems in everyday life. The instrument that indicated the least number of problems was the clinician-reported CPC, with only 21% of participants not having the best outcome that decreased to 8% when using the alternate dichotomization.

When exploring associations between the continuous outcome methods, there were strong associations when comparing the CPC with the performance-based MMSE and the observer-reported IQCODE-CA, and a moderate association between

Table 2. Spearman correlations with confidence intervals (CI) for NFL peak levels at 48 or 72 h post-arrest, and the continuous outcome instruments at 180 days post-arrest.

		95% CI		
	Serum NFL	LL	UL	Degree of association
CPC	0.41	0.32	0.49	Moderate
MMSE	−0.29	−0.38	−0.18	Small
TSQ	−0.16	−0.26	−0.05	Small
IQCODE-CA	0.30	0.20	0.38	Moderate

NFL, neurofilament light chain; LL, lower limit; UL, upper limit; CPC, Cerebral Performance Category; MMSE, Mini-Mental State Examination; TSQ, Two Simple Questions; IQCODE-CA, Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest.

the CPC and the patient-reported TSQ (Figure 3). The association between the patient-reported TSQ and the performance-based MMSE was small.

The agreement on dichotomized outcome for the outcome instruments is shown in Table 5. Moderate agreement was found between the CPC and the MMSE, other agreements were fair.

Discussion

In this explorative study based on a large sample of participants surviving OHCA, we found a significant relation between serum NFL collected in the early phase and results from four methods assessing long-term outcome (clinician-reports, performance-based measures, patient-reports, and observer-reports). We also found associations between the results from all outcome methods assessed at 180 days post-arrest.

NFL is released to the blood early after cardiac arrest and this continues during the first days as a measure of axonal damage due to the ongoing hypoxic-ischemic brain injury (8,9). In the first analyses of this study, we used serum NFL to explore to which extent the four outcome methods reflect such injury. Our group has previously reported that a predictor model with serum NFL and the clinical variables age, sex, time to ROSC, bystander cardiopulmonary resuscitation, and serum lactate at admission had an increased predictive validity for long-term outcome measured by the CPC, compared to using these clinical variables alone (8). In the present study, the small to moderate associations and relationships to all outcome instruments in the unadjusted regression models suggest that the level of acute brain injury inflicted by the circulatory standstill is relevant for evaluating long-term outcome following cardiac arrest, but to varying degrees. According to the ROC analyses, serum NFL was a fair predictor for good long-term outcome using the CPC, which increased to an excellent predictability when applying more permissive dichotomizations. The CPC comes across as the instrument that is best related to brain injury, and this could be attributable to the clinician's summary of all other outcome data. Even so, our results do not suggest that the CPC alone should be used to assess neurocognitive outcome after cardiac arrest. The CPC is criticized for lacking granularity and has a limited value in discriminating between mild and moderate brain injury (24). Accordingly, less problems were indicated when using the CPC compared to other instruments in the current study. Other sequelae of hypoxic-ischemic brain injury, such as emotional problems and fatigue that could impact the HRQoL and cognitive performance in everyday life, may also not be accounted for by the CPC.

In the adjusted regression models, age had a significant association with NFL levels and all outcome instruments. High NFL levels and lower scores on the MMSE are associated with older age (27,34). The overall prevalence of comorbidities is lower than expected in our cohort, possibly due to undiagnosed and unreported risk factors prior to hospital admission. The cardiovascular risk factors were only significate covariates when NFL levels were used to predict outcome on the MMSE, in line with associations with subtle neurocognitive decline in earlier studies (14). The original MMSE exhibits several limitations such as not adjusting for premorbid intelligence and age

Table 3. Regression models for $\log_{10}$-transformed serum NFL peak levels at 48 or 72 h post-arrest, predicting poor outcome on the outcome instruments at 180 days post-arrest.

	Unadjusted models		Age adjusted models		Models adjusted for demographics, cardiovascular risk factors, vitality and mental health*	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
CPC 1 vs. 2–4	8.3 (4.9–14.5)	<0.001	8.3 (4.9–14.7)	<0.001	7.4 (3.6–16.1)	<0.001
CPC 1–2 vs. 3–4	24.6 (10.7–66.4)	<0.001	37.2 (14.3–119.6)[a]	<0.001	67.5 (12.8–694.4)[a,b]	<0.001
MMSE	4.2 (2.7–6.8)	<0.001	3.6 (2.4–5.7)[a]	<0.001	3.6 (2.0–6.4)[c,d,e,f]	<0.001
TSQ question two	2.4 (1.6–3.6)	<0.001	3.0 (2.0–4.7)[g]	<0.001	1.7 (1.0–3.1)[a,b,e]	0.06
IQCODE-CA	3.3 (2.3–4.8)	<0.001	3.5 (2.4–5.2)	<0.001	2.5 (1.5–4.2)[b,h]	<0.001

*Models adjusted for age, sex, level of education, previous diabetes, previous arterial hypertension, previous ischemic heart disease, previous acute myocardial infarction, and/or previous coronary artery bypass grafting, vitality and mental health.

[a] $p < 0.01$ for age

[b] $p < 0.05$ for vitality

[c] $p < 0.05$ for level of education

[d] $p < 0.001$ for age

[e] $p < 0.001$ for mental health

[f] $p < 0.05$ for previous ischemic heart disease, previous acute myocardial infarction, and/or previous coronary artery bypass grafting

[g] $p < 0.05$ for age

[h] $p < 0.05$ for mental health

NFL, neurofilament light chain; CI, Confidence Interval; CPC, Cerebral Performance Category; MMSE, Mini-Mental State Examination; TSQ, Two Simple Questions; IQCODE-CA, Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest.

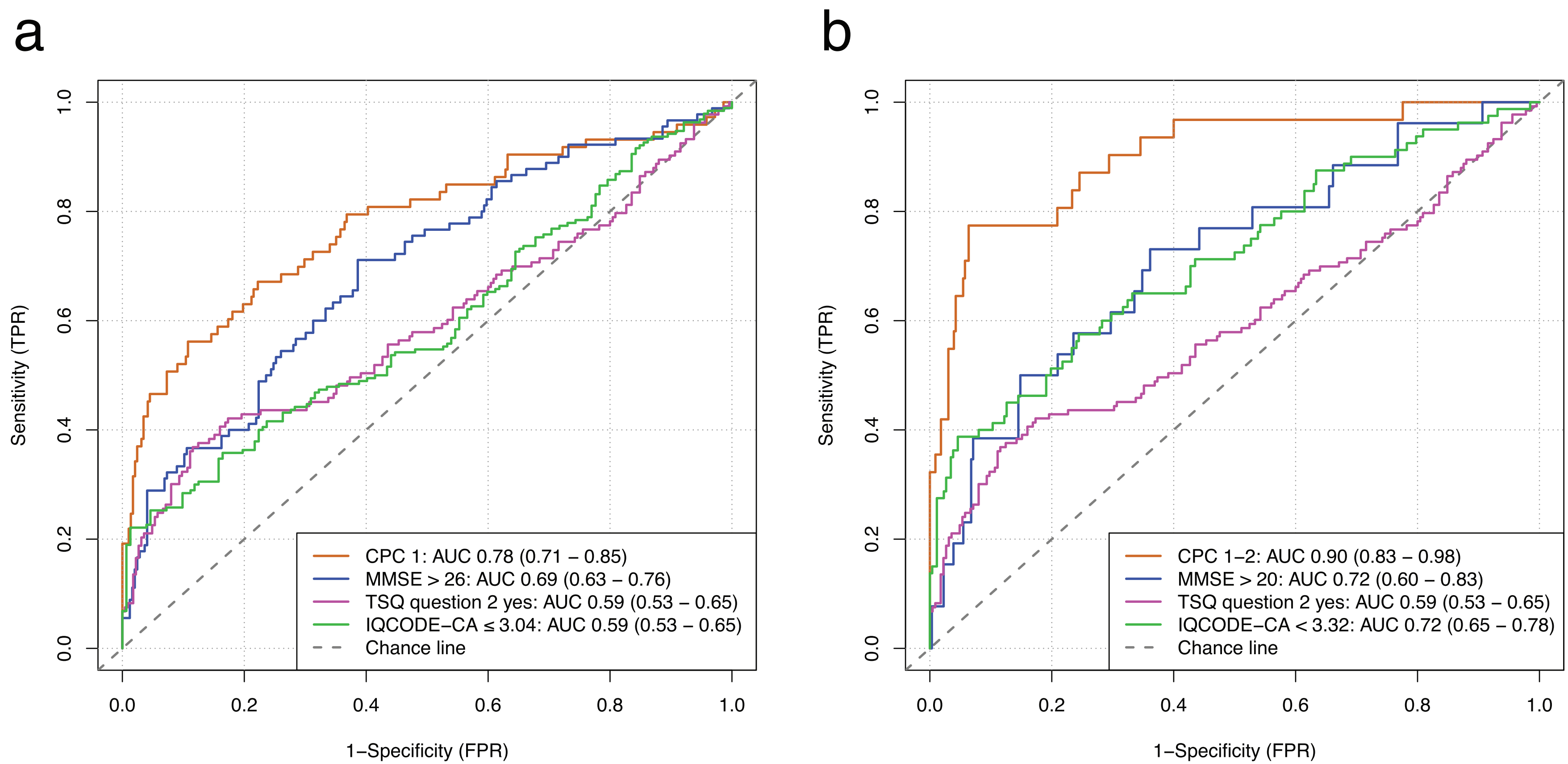

Figure 2. A. CPC 1 vs. CPC 2–4, MMSE > 26, IQCODE-CA ≤ 3.04 cut-scores, representing no–mild brain injury. B. CPC 1–2 vs. CPC 3–4, MMSE > 20, IQCODE-CA < 3.32 cut-scores, representing no–moderate brain injury. Receiver-operating characteristics (ROC) curves for serum neurofilament light chain (NFL) as independent variable, comparing its relation to dichotomized good outcome scores at 180 days post-arrest in participants surviving out-of-hospital cardiac arrest. NFL peak levels at 48 or 72 h post-arrest were used. Area under the curve (AUC) ratios with 95% confidence intervals in parentheses. TPR, True positive rate; FPR, False positive rate; CPC, Cerebral Performance Category; MMSE, Mini-Mental State Examination; TSQ, Two Simple Questions; IQCODE-CA, Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest.

Table 4. Scores on the outcome instruments used in this study, at follow-up 180 days post-arrest (N = 457).

	n (%) or median (Q_1–Q_3)	Missing, n (%)
CPC, median (Q_1–Q_3)	1 (1–1)	0 (0)
Min–Max	1–4	
1, n (%)	360 (79)	
2, n (%)	61 (13)	
3, n (%)	29 (6)	
4, n (%)	7 (2)	
MMSE, median (Q_1–Q_3)	29 (26–30)	45 (10)
Min–Max	2–30	
27–30, n (%)	298 (72)	
21–26, n (%)	85 (21)	
0–20, n (%)	29 (7)	
TSQ question two	0–1	4 (1)
Min–Max		
Yes (complete mental recovery), n (%)	295 (65)	
No (no complete mental recovery), n (%)	158 (33)	
IQCODE-CA, median (Q_1–Q_3)	3.08 (3.00–3.31)	22 (5)
Min–Max	1.42–5.00	
0–3.04, n (%)	20 (48)	
3.05–3.31, n (%)	130 (30)	
3.32–5, n (%)	97 (22)	

Q_1–Q_3, quartile 1 to quartile 3; CPC, Cerebral Performance Category; MMSE, Mini-Mental State Examination; TSQ, Two Simple Questions; IQCODE-CA, Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest.

(37). In our study, a high level of education was also associated with higher MMSE scores and vice versa, suggesting that the instrument reflects vascular burden and educational attainment as well as current cognitive status.

Vitality and mental health had a significant effect on the outcome methods. These factors were stronger predictors for patient-reported outcome on the TSQ than hypoxic-ischemic brain injury according to NFL, rendering NFL statistically non-significant in this analysis. Patient-reported outcome measures provide a unique perspective on the patient's own experience, and are recommended for assessing HRQoL after cardiac arrest (38). The interpretation of "mental recovery," the central construct of the TSQ, could however be broad, subjective, and may cause a discrepancy among raters. The Vitality domain from the SF-36v2® has been found to correlate strongly with a fatigue rating scale in a cohort of individuals post-OHCA (39), and fatigue is a common complaint following cardiac arrest (40). The significant effect of vitality and mental health on the TSQ imply that it is influenced by fatigue and emotional problems rather than brain injury measured by NFL. This reflects that fatigue and emotional problems are important factors for the long-term outcome post-arrest. The results further propose that patient-reported outcome

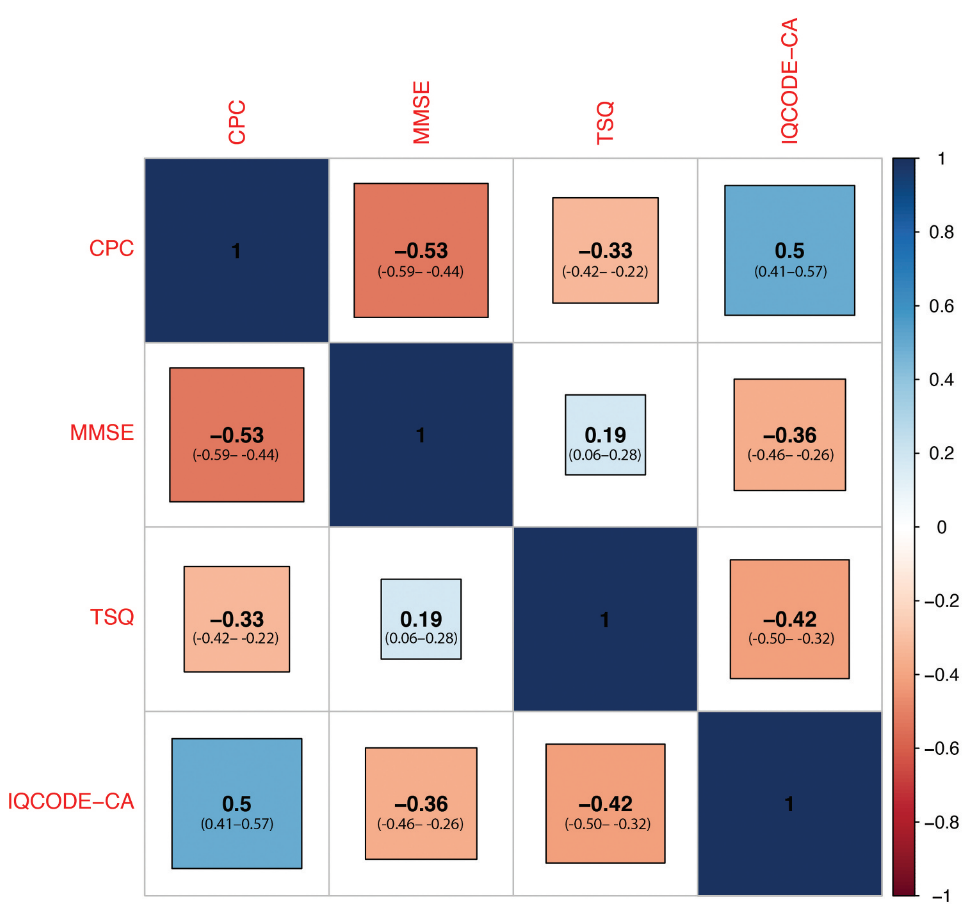

Figure 3. Correlation matrix for the full-scale continuous outcome instruments at 180 days post-arrest, calculated with Spearman's rho. Confidence intervals, 95%, in parentheses. CPC, Cerebral Performance Category; MMSE, Mini-Mental State Examination; TSQ, Two Simple Questions; IQCODE-CA, Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest.

Table 5. Pairwise unweighted kappa and percent agreement for the dichotomized outcome instruments representing no–mild brain injury ($N = 457$).

	Kappa (95% CI)	Strength of agreement	Percent agreement	Missing, n (%)
CPC–MMSE	0.50 (0.40–0.60)	Moderate	82	45 (10)
CPC–TSQ	0.30 (0.21–0.39)	Fair	71	4 (1)
CPC–IQCODE-CA	0.27 (0.20–0.34)	Fair	63	22 (5)
MMSE–TSQ	0.21 (0.12–0.31)	Fair	67	45 (10)
MMSE–IQCODE-CA	0.24 (0.15–0.32)	Fair	62	64 (14)
TSQ–IQCODE-CA	0.30 (0.22–0.39)	Fair	65	26 (6)

CI, Confidence Interval; CPC, Cerebral Performance Category; MMSE, Mini-Mental State Examination; TSQ, Two Simple Questions; IQCODE-CA, Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest.

might be influenced by rehabilitation interventions such as fatigue management and treatment for emotional problems. These areas could be targeted in patient-centered, interdisciplinary neuropsychological rehabilitation which is effective in a variety of cognitive and functional disabilities after brain injury (41). Future studies on NFL and neurocognitive outcome are recommended to use measurements of fatigue and emotional problems with improved granularity, and to control for neuropsychological rehabilitation.

Our second aim was to investigate to what extent the outcome methods overlap. The lowest association was found between the performance-based MMSE and the patient-reported TSQ (Figure 3; $r_s = 0.19$). The comparability of these two instruments is somewhat limited, as the MMSE consists of 11 items while the TSQ is used as a one-item instrument in this study and lacks thorough psychometric validation. Yet, discrepancies between objective neurocognitive impairment and subjective complaints have been observed using similar instruments in other acquired brain injury cohorts as well (10). The small–moderate but not perfect associations between the four methods suggests acceptable convergent validity (42), and that they may be combined when assessing neurocognitive outcome post-arrest.

When comparing the degree of agreement between the dichotomized outcome instruments, we found the greatest agreement between the clinician-report CPC and the performance-based screening MMSE. MMSE can indicate major neurocognitive disorder with adequate sensitivity but is less sensitive for mild symptoms, especially in individuals with an initially high neurocognitive performance prior to cardiac arrest. Thus, ceiling effects is a shared trait between the CPC and MMSE, possibly a contributing factor of the high degree of agreement between these measures when dichotomized.

Knowledge about what the instruments for each outcome method represent is essential when developing follow-up models, identifying patients that may need an extensive neuropsychological assessment, and when measuring the efficacy of clinical trials. The instruments should have acceptable levels of validity, reliability, and feasibility to reflect outcome in everyday life. Each of the outcome methods in this study are suggested to provide information on neurocognitive and neurological functional performance, but use different methods. The TSQ and IQCODE-CA are designed to investigate everyday problems related to cognitive function post-arrest, while the MMSE was designed as a practical test for grading cognition in patients with neurodegenerative disorders (26), and indicates current cognitive performance without a baseline prior to the arrest. The CPC takes all other available patient data, including other instruments, into account but is dependent on correct information about the patient, accurate clinical judgment, and a standardized scale for acceptable inter-rater reliability. Hypoxic-ischemic brain injury represented by serum NFL is the common denominator of all these methods in this study, the instruments might however also reflect possibly confounding factors such as demographic factors or cardiovascular decline to a varying degree.

The strengths of the present study are the large sample size from an international multicenter study and the detailed data on brain injury following OHCA, both in the acute phase and concerning the long-term outcome. Moreover, results from the outcome measures are combined with data on NFL, the best proxy biomarker for hypoxic-ischemic brain injury after cardiac arrest to date (9).

This exploratory study also has several limitations. The sensitivity of the outcome instruments in this study can be questioned, with potential ceiling effects on the CPC and MMSE demonstrated by only 8% of long-term surviving participants having a really poor outcome on the CPC. Accordingly, it is possible that serum NFL would predict outcome even better using more sensitive instruments. Instead of the CPC and MMSE, the modified Rankin Scale and Montreal Cognitive Screening Assessment are currently suggested as these instruments have increased discriminatory abilities between levels of mild and moderate dysfunction (1,38). Future studies could examine instrument predictability on participation and return to work, to further improve diagnostic and ecological validity, i.e., the predictive relationship to the patient's behavior in a variety of everyday settings. Furthermore, the investigation of which outcome instruments that are most associated with NFL release has been a methodological challenge. The outcome data were based on different scales; to increase the comparability, we dichotomized the data in some analyses.

Conclusions

Serum NFL exhibited small to moderate associations and a significant relation to CPC, MMSE, TSQ, and IQCODE-CA in a large sample of long-term surviving participants following OHCA. All outcome methods do not appear to reflect initial hypoxic-ischemic brain injury to the same extent; the CPC correlated best with NFL, i.e., neuronal injury, but exhibited a ceiling effect. We found correlations ranging from small to strong between all outcome methods. Our findings may be employed when selecting methods and instruments for clinical follow-up models, used to identify patients in need of further neurological rehabilitation after OHCA.

Disclosure statement

K.B. has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, 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, all unrelated to the present work. J.K. is supported by a grant from NovoNordisk foundation (grant number NNF17OC0028706), for work outside the present manuscript. H.Z. has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, all unrelated to the present work. H.Z. is a Wallenberg Scholar. All other authors report no conflicts of interest with respect to the research, authorship, and/or publication of this article. The study sponsors had no involvement in the study design; in the collection, analyses and interpretation of the data; in the writing of the manuscript or in the decision to submit the manuscript for publication.

Funding

This work was supported by the the Swedish state under the agreement between the Swedish government and the County Councils – the ALF-agreement [ALFGBG-715986,ALFGBG-720931];The Swedish Research Council;The Swedish Society of Medicine;The County Council of Skane; The Segerfalk Foundation;The Hans-Gabriel and Alice Trolle-Wachtmeister Foundation for Medical Research;The Koch Foundation; The Tryg Foundation;The Swedish Heart and Lung Association;The Royal Swedish Academy of Sciences;The Skane University Hospital Psychology Research and Development Grant;The Skane University Hospital Foundations;The Swedish Heart-Lung Foundation;The Gyllenstiernska-Krapperup Foundation;AFA Insurance Foundation;Academy of Caring Sciences at Skane University Hospital.

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