Supplemental Online Content

Hoiland RL, Rikhraj KJK, Thiara S, et al. Neurologic prognostication after cardiac arrest using brain biomarkers: a systematic review and meta-analysis. *JAMA Neurol*. Published online February 28, 2022. doi: 10.1001/jamaneurol.2021.5598

This supplementary material has been provided by the authors to give readers additional information about their work.

Appendix 1: Detailed Methods

Literature Search

We searched the following electronic databases from inception to September 15th, 2021. MEDLINE, Embase, Evidence-Based Medicine Reviews, CINAHL, Cochrane Database and the WHO Global Health Library. We also searched the Cochrane Central Register of Controlled Trials, BioMed Central, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform and Thomson Center Watch for unpublished works.

Search Terms

We used two subsets of search terms. The first included studies that identified biomarkers of interest: “biomarker,” “neuron specific enolase,” “NSE,” “S100 beta,” “S100 calcium binding protein,” “glial fibrillary protein,” “GFAP,” “neurofilament-light,” “Nf-L,” “Tau,” “ubiquitin carboxyl hydrolase L1” and “UCH-L1.” The second included studies with the following terms: “cardiac arrest,” “post cardiac arrest,” “hypoxic ischemic brain injury,” “anoxic brain injury,” “ROSC,” and “return of spontaneous circulation.” The two search terms were combined using “AND” to identify relevant studies. See Appendix 2 for the MEDLINE search strategy.

Modification of inclusion criteria

Upon review of the literature we felt it necessary to include additional time points for outcome determination that were not specified within the PROSPERO registration, which was restricted to hospital discharge and 6-months. This was due to the large amount of studies and thus patients wherein outcome determination was not made strictly at hospital discharge or at 6-

months but instead in between those time points. We have provided a table (eTable 4) outlining the specific studies that assessed outcomes at time points that differed from hospital discharge or 6-months. As noted in the final row of eTable 4, 36 studies (41% of all studies) and 5495 patients (52% of all patients) performed outcome determination at a time differing from hospital discharge and 6-months. Exclusion of these studies would have significantly limited this systematic review and meta-analysis by reducing the sample size by ~50%. Further, to increase generalizability and provide data to inform clinicians / patients, we included time points between discharge and 6-months to provide outcome time points that could enrich the findings by increasing the longitudinal timing of outcome determination. Similarly, we felt it appropriate to include studies that used survival versus death as their outcome as this comprised 9 studies (10% of all studies) and 741 patients (7% of all patients), which is outlined in eTable 5.

Additional exclusion criteria

We excluded studies that did not: 1) dichotomize neurological outcomes; 2) specify timing of bio-specimen collection or outcome determination; 3) report diagnostic test accuracy, biomarker concentration or did not report data compatible for extraction (e.g. figures that cannot be accurately digitized).

Study Selection

Using a two-stage selection process, two reviewers (RH and KR) independently screened abstracts using the inclusion and exclusion criteria. If the abstract was unavailable, the full text was reviewed instead. Following abstract screening, the reviewers independently reviewed each identified full text before collaboratively making decisions on study inclusion. Disagreements regarding study inclusions were resolved by a third reviewer (MS).

Data Extraction & Quality Assessment

Four reviewers (RH, KR, ST and MS) used a pre-formatted spreadsheet (Microsoft Excel®, Redmond Washington, USA) to collect data on the study design, inclusion and exclusion criteria, brain biomarkers levels, diagnostic test accuracy, and neurological outcome. Study quality was assessed by two reviewers (RH and KR) using the QUADAS-2 scale. Studies were rated on their risk of bias and applicability in four domains: patient selection, index test, reference standard, and flow and timing.

Appendix 2: Search strategy for MEDLINE

MEDLINE

1. Biomarker.mp.
2. Neuron specific enolase.mp.
3. NSE.mp.
4. S100 beta.mp.
5. S100 calcium binding protein.mp.
6. Glial fibrillary protein.mp.
7. GFAP.mp.
8. Neurofilament-light.mp.
9. Nf-L.mp.
10. Tau.mp.
11. Ubiquitin Carboxyl Hydrolase L1.mp
12. UCH-L1.mp.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. Cardiac arrest.mp.
15. Post cardiac arrest.mp.
16. Hypoxic ischemic brain injury.mp.
17. Anoxic brain injury.mp.
18. ROSC.mp.
19. Return of spontaneous circulation.mp.
20. 14 or 15 or 16 or 17 or 18 or 19
21. 13 and 20

Appendix 3: Outline of data inclusion for studies with duplicated data.

Data that were duplicated across more than one publication were not duplicated across our analysis, nor in our summary data in Table 1. However, publications with duplicated data that reported their data in a different fashion (ROC curves versus group summary statistics) or for different time points may have contributed to different aspects of this meta-analysis. Groups of publications with duplicated data are outlined below and the specific data from each is noted:

TTM studies:

Stammet *et al.,* 2015. *Journal of the American College of Cardiology*:

- NSE: Summary statistics (median±IQR) at 24hr, 48hr and 72hr
- NSE: ROC data at 24hr, 48hr, and 72hr

Mattsson *et al.,* 2017. *Annals of Neurology*:

- Tau: Summary statistics (median±IQR) at 24hr, 48hr and 72hr
- Tau: ROC data at 24hr, 48hr, and 72hr

Stammet *et al.,* 2017. *Critical Care*:

- S100B: Summary statistics (median±IQR) at 24hr, 48hr, and 72hr
- S100B: ROC data at 24hr, 48hr and 72hr

Moseby-Knappe *et al.,* 2019. *JAMA Neurology*:

- Nf-L: Summary statistics (median±IQR) at 24hr, 48hr and 72hr
- Nf-L: ROC data at 24hr, 48hr, and 72hr

Stefanizzi *et al.,* 2020. *International Journal of Molecular Sciences*:

- No data contributed to meta-analysis

Ebner *et al.,* 2020. *Resuscitation*:

- GFAP: Summary statistics (median±IQR) at 24hr, 48hr, 72hr
- GFAP: ROC data at 24hr, 48hr and 72hr
- UCH-L1: Summary statistics (median±IQR) at 24hr, 48hr, 72hr
- UCH-L1: ROC data at 24hr, 48hr and 72hr

Moseby-Knappe *et al.,* 2021. *Intensive Care Medicine*:

- No data contributed to meta-analysis

<u>COMACARE studies:</u>

Jakkula *et al.,* 2019. *Critical Care*:

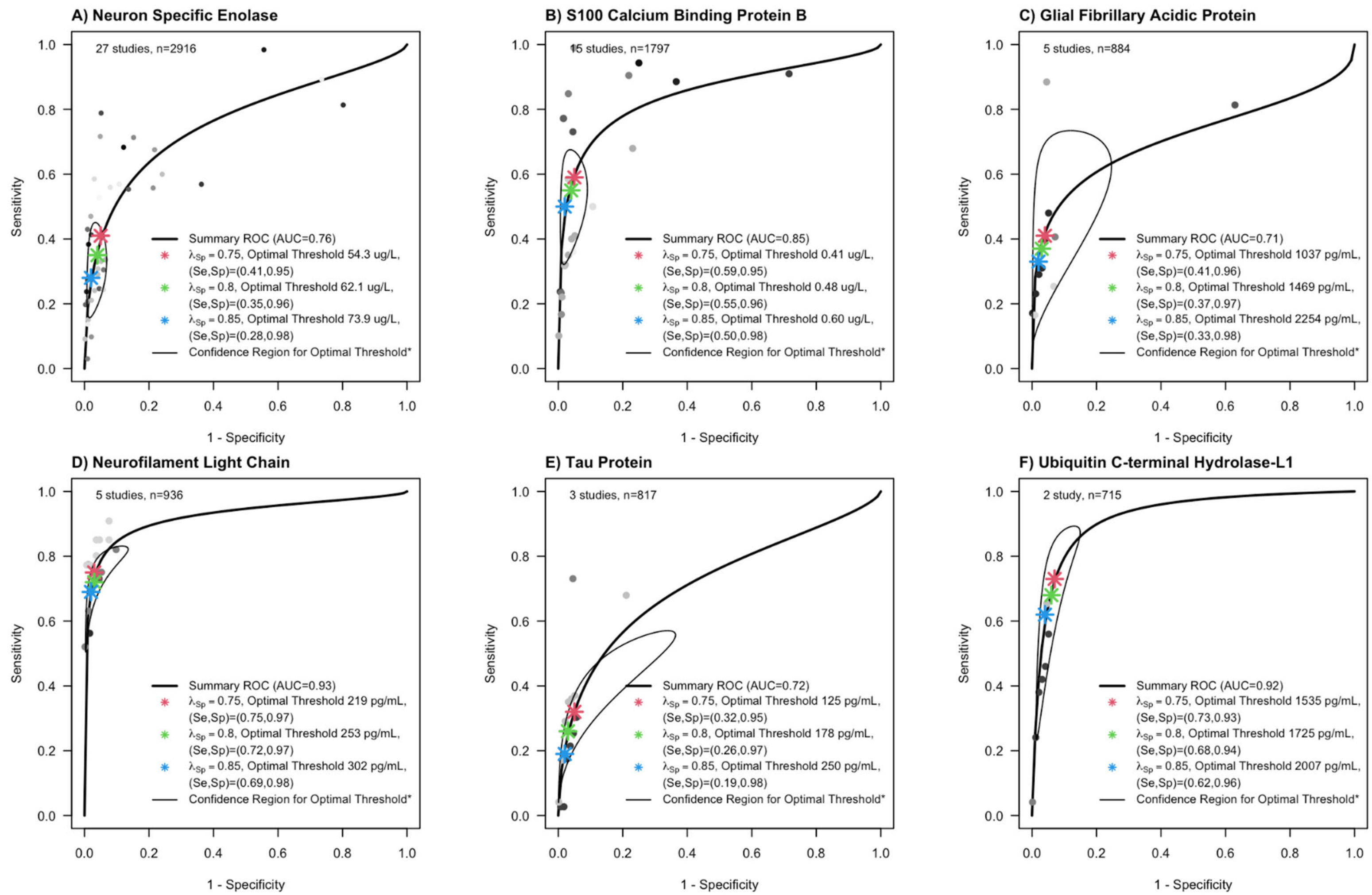
- NSE: Summary statistics (median±IQR) at 48hr

Wihersaari *et al.,* 2021. *Intensive Care Medicine*:

- Nf-L: Summary statistics (median±IQR) at 24hr, 48hr and 72hr
- Nf-L: ROC data at 0hr, 24hr, 48hr, and 72hr

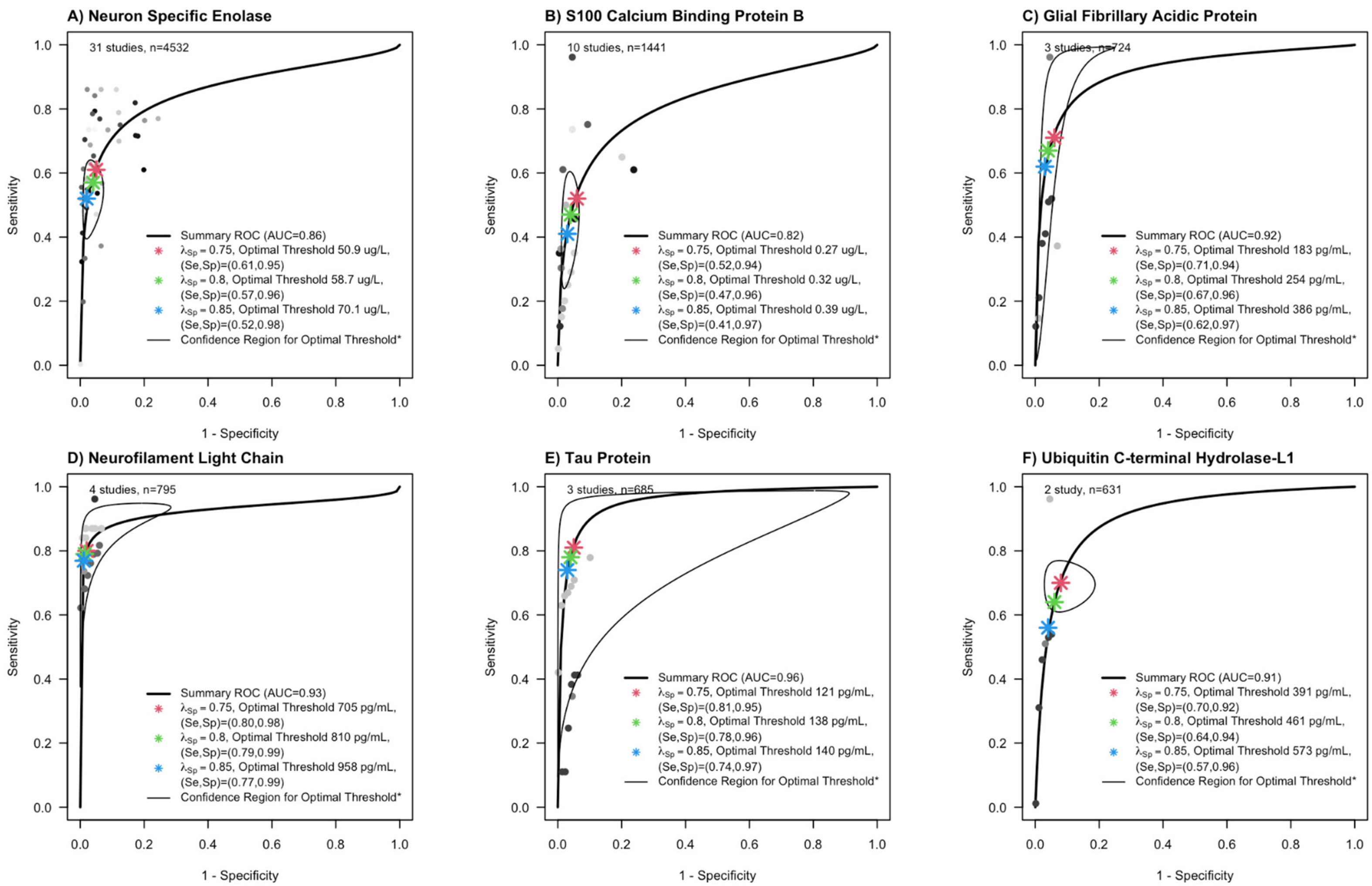
Appendix 4: QUADAS-2 results

It was determined that for patient selection 31% of studies had a low risk of bias, 54% had a high risk of bias, and the risk of bias was unclear in 15% of studies. Studies most commonly were assigned a high risk of bias because they did not avoid inappropriate patient exclusion. For the index test (biomarkers), it was unclear (i.e. not specified) in 54% of studies if results were interpreted without the knowledge of the reference standard (clinical outcomes), while it was unclear (i.e. not specified) in 51% of studies if results of the reference standard were interpreted without the knowledge of the index test. Risk of bias was determined to be low for 43% of studies regarding the index test category and for 44% of studies regarding the reference standard category. Risk of bias related to flow and timing was high for 44% of studies, where the interval between the index test (biomarkers) and reference standard (neurological outcome) was determined as not appropriate in 40% of studies. Overall, the concerns of applicability were low in 92% of studies for patient selection, 92% of studies for the index test, and 94% of studies for the reference standard (See eFigure 7).



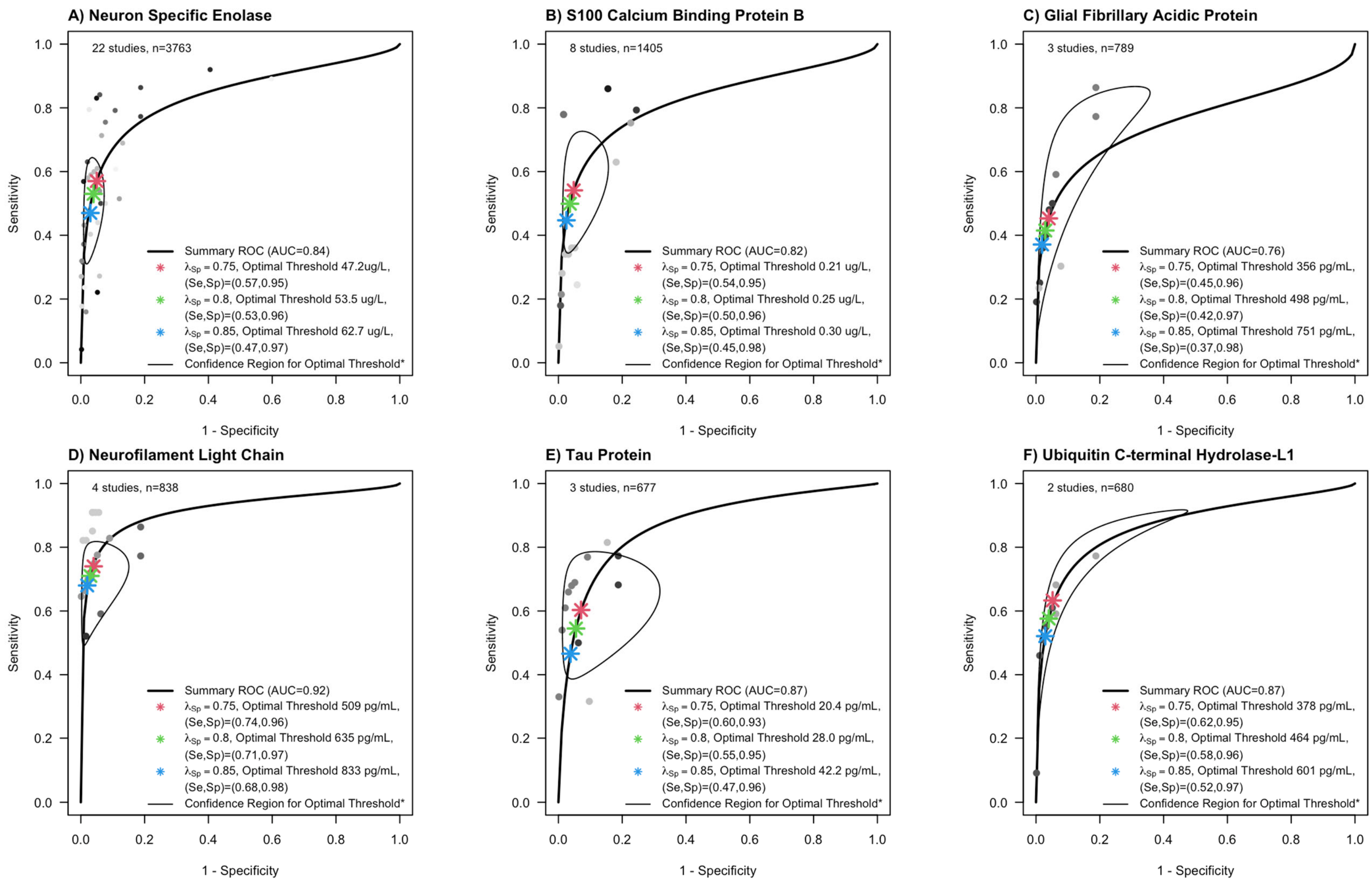
eFigure 1. Receiver Operator Characteristic Curves for the Diagnostic Accuracy of Brain Biomarkers Post ROSC for Predicting Unfavorable Outcome at 24 hours. Summary receiver operator characteristic (SROC) curves and their confidence intervals for each biomarker at 24 hours post return of spontaneous circulation (ROSC) are presented. Each individual black/grey dot represents a unique study. We estimated optimal thresholds for each biomarker for particular weights of specificity. We weighted specificity at 75% (red symbols), 80% (green symbols), and 85% (blue symbols) with sensitivity weighted 25%, 20%, and 15% respectively. For each weight of specificity an optimal threshold on the SROC curve was determined and is reported in the figure for each variable. The

SROC AUC and 95% confidence intervals for each biomarker are: NSE- 0.76 (0.66-0.84); S100b- 0.85 (0.77-0.91); GFAP- 0.71 (0.42-0.90); NFL- 0.93 (0.87-0.95); Tau- 0.72 (0.46-0.90); UCH-L1- 0.92 (0.69-0.97).



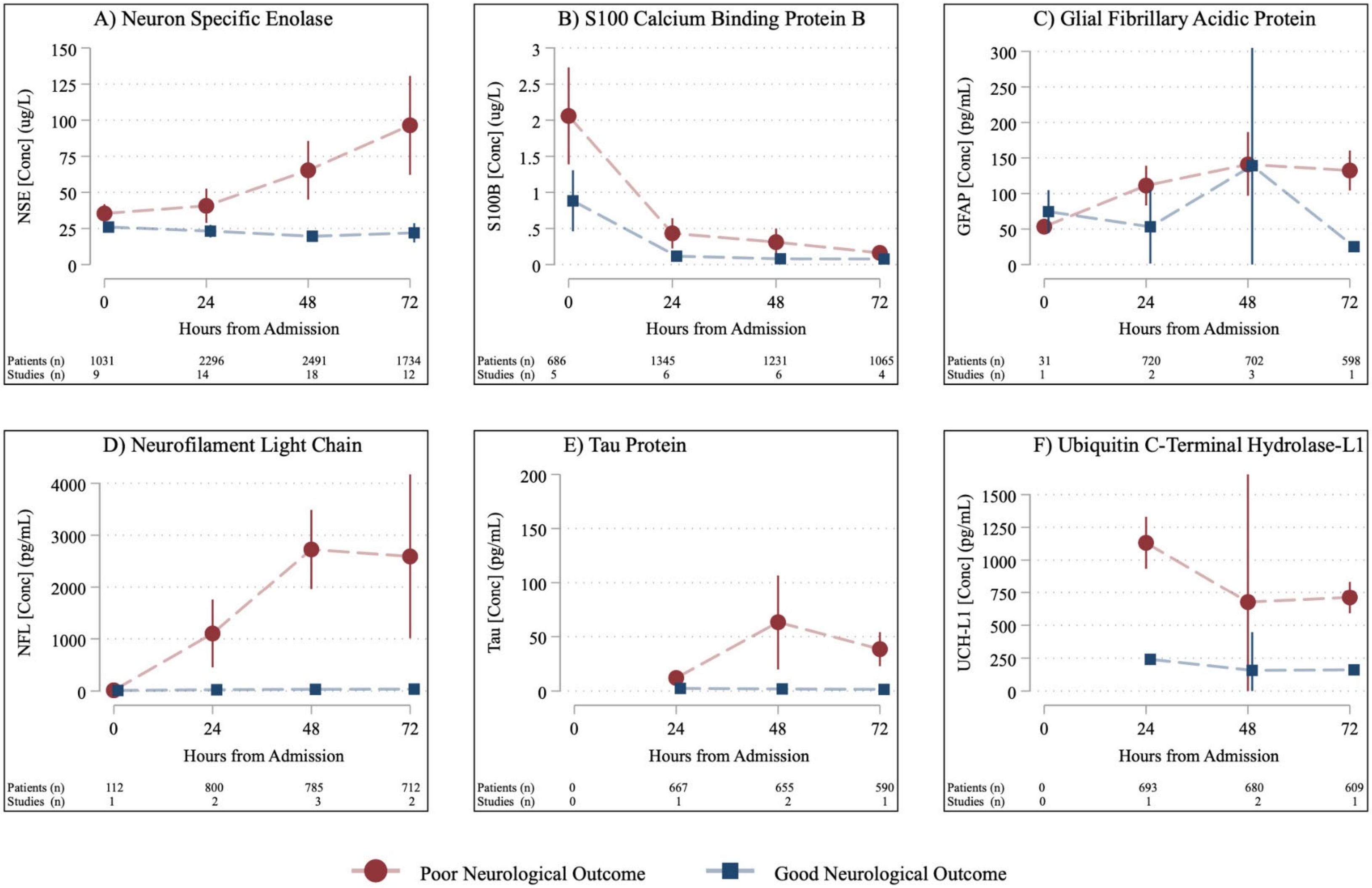
eFigure 2. Receiver Operator Characteristic Curves for the Diagnostic Accuracy of Brain Biomarkers Post ROSC for Predicting Unfavorable Outcome at 72 hours. Summary receiver operator characteristic (SROC) curves and their confidence intervals for each biomarker at 72 hours post return of spontaneous circulation (ROSC) are presented. Each individual black/grey dot represents a unique study. We estimated optimal thresholds for each biomarker for particular weights of specificity. We weighted specificity at 75% (red symbols), 80% (green symbols), and 85% (blue symbols) with sensitivity weighted 25%, 20%, and 15% respectively. For each weight of specificity an optimal threshold on the SROC curve was determined and is reported in the figure for each variable. The

SROC AUC and 95% confidence intervals for each biomarker are: NSE- 0.86 (0.80-0.90); S100b- 0.82 (0.72-0.90); GFAP- 0.92 (0.40-0.99); NFL- 0.93 (0.87-0.96); Tau- 0.96 (0.22-0.99); UCH-L1- 0.91 (0.81-0.93).



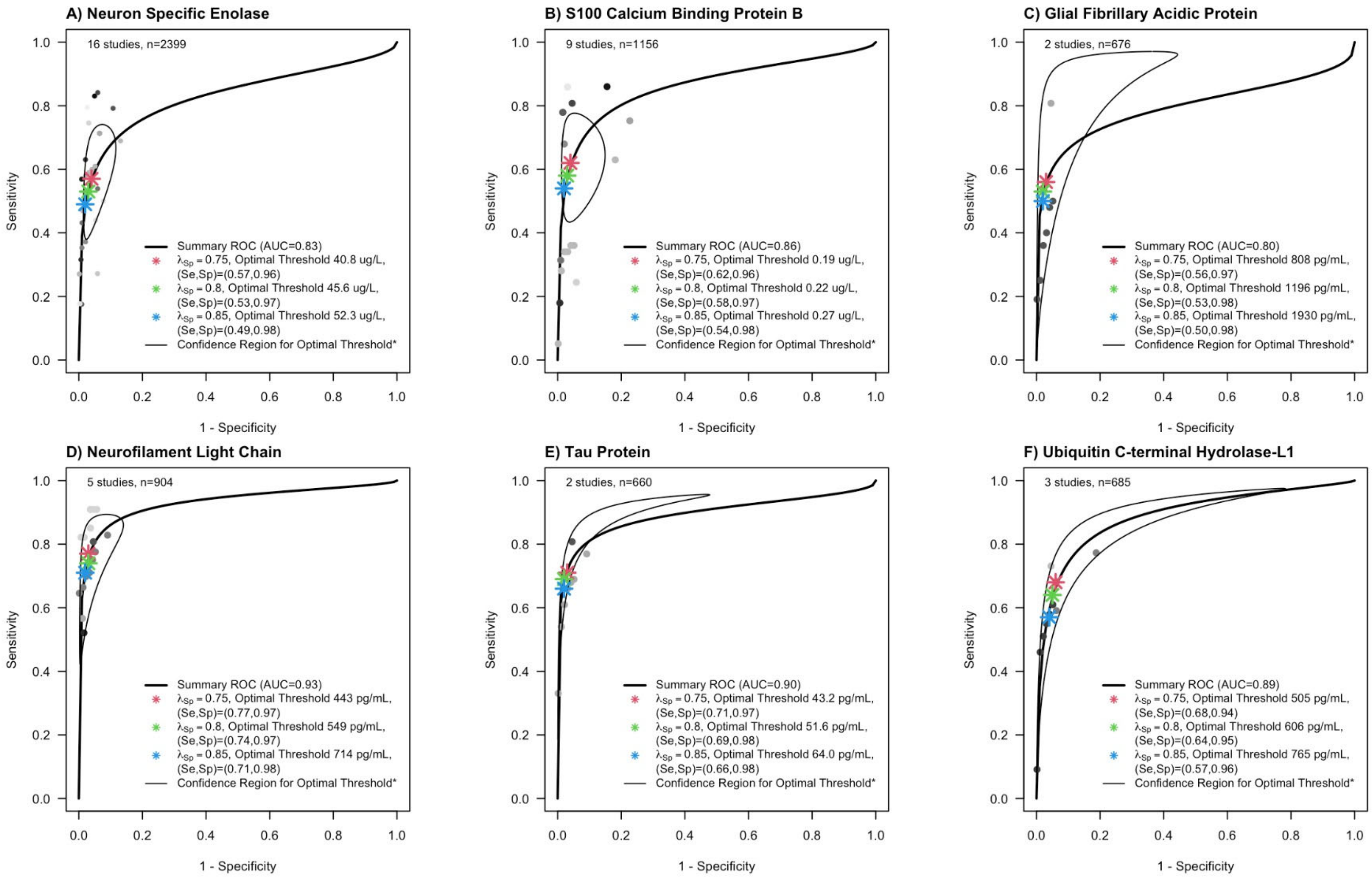
eFigure 3. Receiver Operator Characteristic Curves for the Diagnostic Accuracy of Brain Biomarkers for Predicting Unfavorable outcome at 48 hours in patients that underwent targeted temperature management. Summary receiver operator characteristic (SROC) curves and their confidence intervals for each biomarker are presented. Each individual black/grey dot represents a unique study. We estimated optimal thresholds for each biomarker for particular weights of specificity. We weighted specificity at 75% (red symbols), 80% (green symbols), and 85% (blue symbols) with sensitivity weighted 25%, 20%, and 15%

respectively. For each weight of specificity an optimal threshold on the SROC curve was determined and is reported in the figure for each variable. The SROC AUC and 95% confidence intervals for each biomarker are: NSE- 0.84 (0.77-0.90); S100b- 0.82 (0.72-0.90); GFAP- 0.76 (0.42-0.93); NFL- 0.92 (0.86-0.95); Tau-0.87 (0.80-0.92); UCH-L1- 0.87 (0.41-0.97).



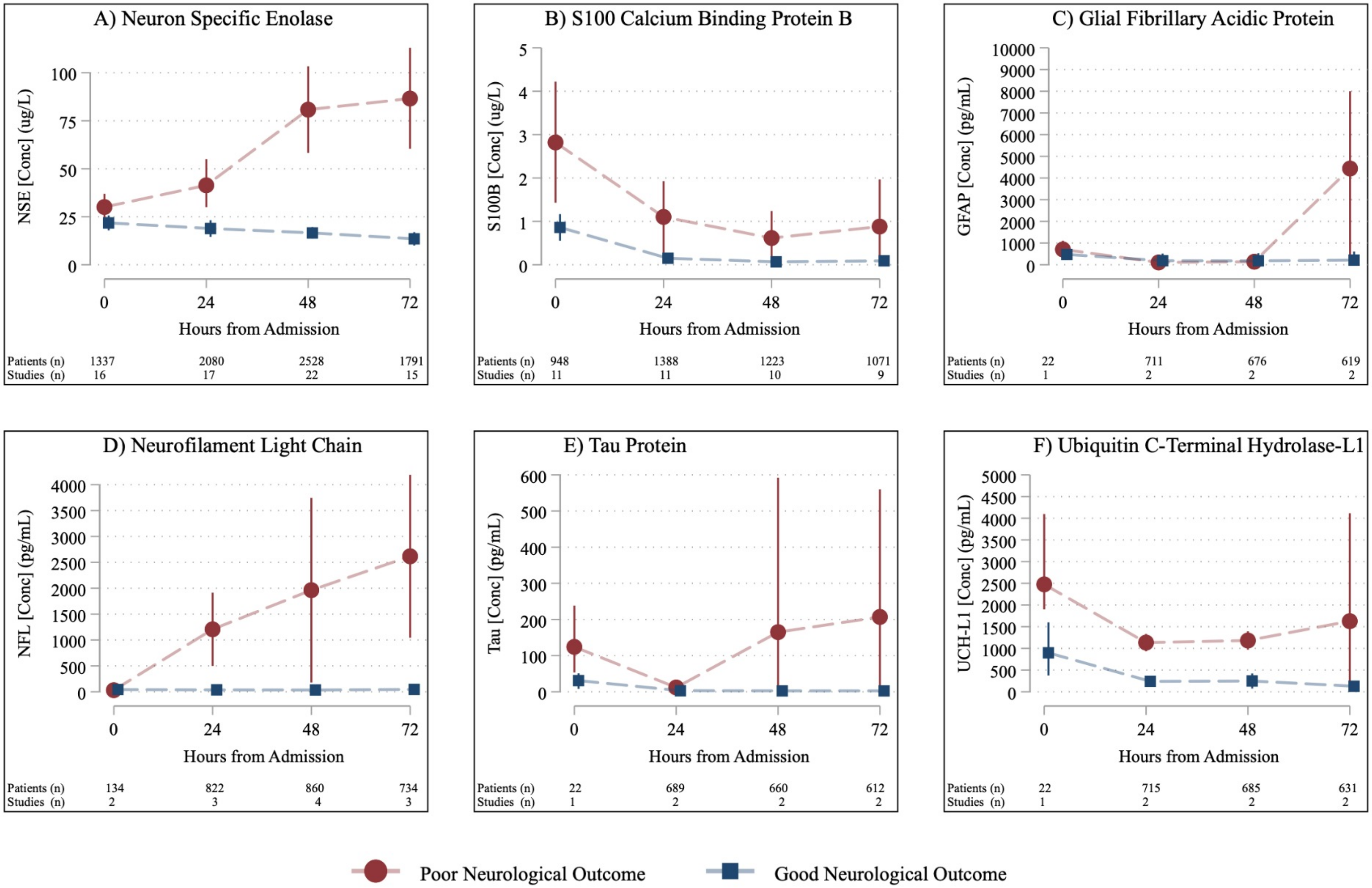
eFigure 4. Group Differences in Brain Biomarkers Between Patients That Underwent TTM with Favorable and Unfavorable Neurological Outcome. The median concentration and spread (interquartile range) are reported in patients with favorable (blue squares) and unfavorable (red circles) outcome at 0, 24,

48, and 72 hours following admission. The number of patients and studies included in the determination of the median and interquartile range for each time point is noted within each graph.



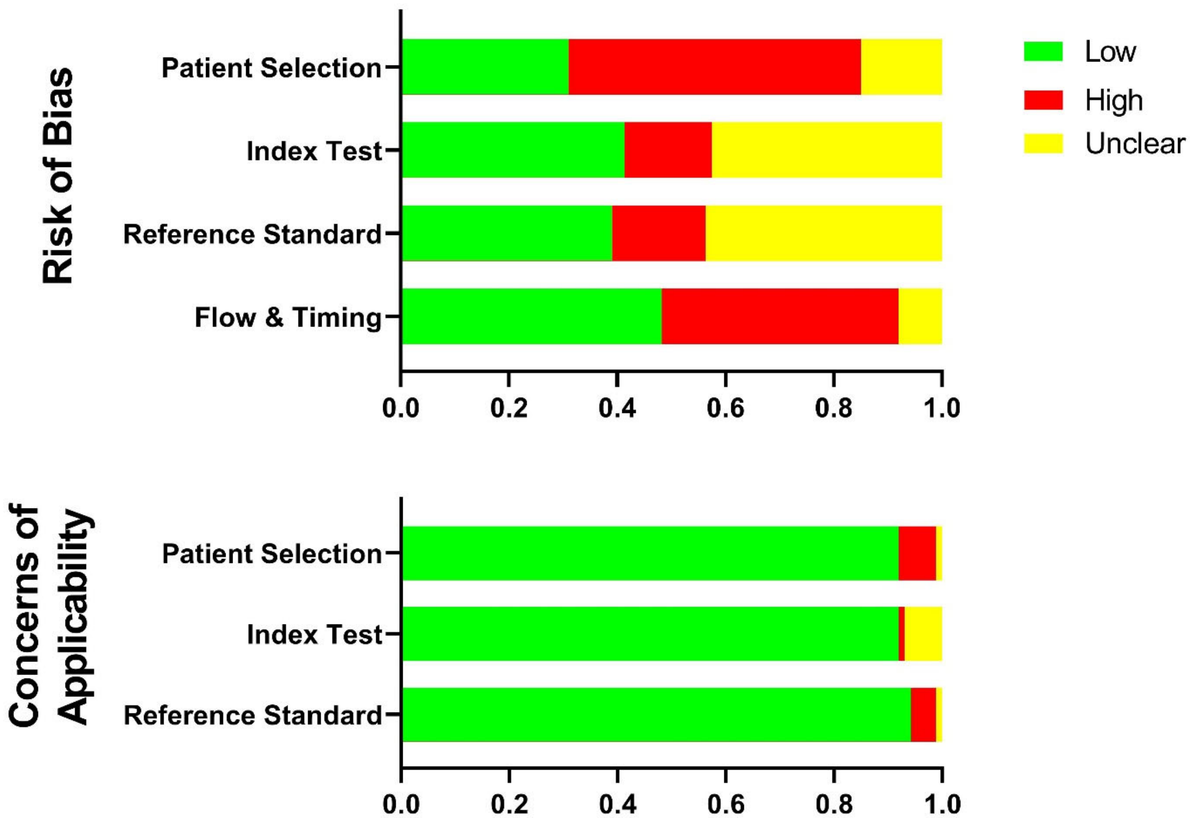
eFigure 5. Receiver Operator Characteristic Curves for the Diagnostic Accuracy of Brain Biomarkers for Predicting Unfavorable outcome at 48 hours in patients that had an out-of-hospital cardiac arrest. Summary receiver operator characteristic (SROC) curves and their confidence intervals for each biomarker are presented. Each individual black/grey dot represents a unique study. We estimated optimal thresholds for each biomarker for particular weights of specificity. We weighted specificity at 75% (red symbols), 80% (green symbols), and 85% (blue symbols) with sensitivity weighted 25%, 20%, and 15% respectively. For each weight of specificity an optimal threshold on the SROC curve was determined and is reported in the figure for each variable. The SROC AUC and 95%

confidence intervals for each biomarker are: NSE- 0.83 (0.77-0.89); S100b- 0.86 (0.79-0.92); GFAP- 0.80 (0.59-0.92); NFL- 0.93 (0.86-0.97); Tau- 0.90 (0.74-0.97); UCH-L1- 0.89 (0.53-0.99).



eFigure 6. Group Differences in Brain Biomarkers Between Patients That Had an Out-of-Hospital Cardiac Arrest with Favorable and Unfavorable Neurological Outcome. The median concentration and spread (interquartile range) are reported in patients with favorable (blue squares) and unfavorable (red

circles) outcome at 0, 24, 48, and 72 hours following admission. The number of patients and studies included in the determination of the median and interquartile range for each time point is noted within each graph.



eFigure 7. QUADAS-2 assessment for risk of bias and concerns of applicability.

eTable 1. Study Characteristics.

Study	Study Design	Inclusion Criteria	Exclusion Criteria	Biomarkers assessed	Neurologic Scale	Time of outcome determination	Number of patients
Adler et al. 2021[1] PMID: 34328545	Retrospective	Non-traumatic OHCA	Not specified	NSE, Nf-L	CPC 1&2 vs. CPC 3-5	Hospital discharge	53
Akin et al. 2021[2] PMID: 33411836	Retrospective	OHCA patients	Death before 3-days of ICU stay	NSE, S100B	CPC 1&2 vs. CPC 3-5	Day of discharge from either inpatient medical treatment or intensive care neurological rehabilitation,	251
Auer et al. 2006[3] PMID: 17175624	Prospective	ROSC after CPR of at least 5 min; non-traumatic normothermic IHCA or OHCA.	History of cancer before CPR; transfer from other ICUs; non-cardiac etiology for the cardiac arrest.	NSE	Survival	Survival to hospital discharge or death	17
Barbella et al. 2020[4] PMID: 32044334	Retrospective	Adults admitted for cardiac arrest	Not specified	NSE	CPC 1-3 vs. 4&5	3 months post CA	158
Bongiovanni et al. 2020[5] PMID: 32016534	Prospective	All comatose adult patients resuscitated from CA for whom data were available for N20 response on SSEP, complete pupillary and corneal reflexes evaluation, EEG and NSE determination	Brain death within 24h	NSE	CPC 1&2 vs. 3-5	3 months after CA	485

[1]Adler *et al.,* (2021). *J Neurol*. doi: 10.1007/s00415-021-10722-3
[2]Akin *et al.,* (2021). *PLoS One*. 16(1):e0245210
[3]Auer *et al.,* (2006). *CJEM*. 8(1):13-8.
[4]Barbella *et al.,* (2020). *Resuscitation*. 149:17-23
[5]Bongiovanni *et al.,* (2020). *Intensive Care Med*. 46(5):963-972

Bottiger et al. 2001[6] PMID: 11390339	Prospective	Patients who had undergone CPR after nontraumatic cardiac arrest before admission to the hospital and who were covered by the local physician-staffed advanced cardiac life support system	Not specified	NSE, S100B	CPC 1 vs. CPC 4&5	14 days post ROSC	66
Choi et al. 2016[7] PMID: 27287003	Prospective	All cardiac arrest patients with sustained unconsciousness, regardless of location of arrest or initial rhythm,	Age < 18 years old, traumatic arrest, marked signs of infection	NSE, S100B	CPC 1&2 vs. CPC 3-5	Hospital discharge	119
Chung-Esaki et al. 2018[8] PMID: 30145080	Prospective	Adult patients ≥18 years who were resuscitated from cardiac arrest and had persistent coma after return of spontaneous circulation.	Patients with pre-existing DNR orders, pregnancy, terminal or severe coexisting systemic disease limiting life expectancy, active enrollment in experimental drug therapies/procedures which would interfere with the study or lack of surrogate decision maker to provide informed consent.	NSE	GOS 3-5 vs. 1-2	6 months post arrest	98
Clifford-Mobley et al. 2020[9] PMID: 31615270	Prospective	Post-OHCA patients who had serum NSE measured on admission	Death within the first 72h and no subsequent NSE concentration available	NSE	Survival	ICU discharge	142

[6]Bottiger *et al.,* (2001). *Circulation*. 103(22):2694-8.
[7]Choi *et al.,* (2016). *Emerg Med J*. 33(10):690-5
[8]Chung-Esaki *et al.,* (2018). *J Clin Neurosci*. 57:99-104.
[9]Clifford Mobley *et al.* (2020). *Ann Clin Biochem*. 57(1):69-76

Daubin et al. 2011[10] PMID: 21824428	Prospective	Patients who remained in coma at 48 hours after cardiac arrest were included in the analysis	Patients who died or awoke within the first 48 hours of admission were excluded	NSE	CPC 1-3 vs. 4&5	3 months post CA	97
Derwall et al. 2009[11] PMID: 19368739	Prospective	Adults >18 years old suffering from non traumatic out of hospital CA	Sepsis, stroke, previous CPR and cancer in last 6 months	S100B	CPC 1&2 vs. 3-5	14 days post ROSC	68
Deye et al. 2020[12] PMID: 32858156	Prospective	All comatose adult patients ≥18 years old who suffered from non-traumatic and successfully resuscitated CA with sustained ROSC (>20min), hospitalized in ICU and TTM-treated	Conscious patients, without sustained ROSC, refractory CA or cardiogenic shock after CA necessitating ECLS, DNR order and patients without any S100B values measured	NSE, S100B	CPC 1&2 vs. 3-5	At hospital discharge and 3 months after CA	330
Disanto et al. 2019[13] PMID: 31375414	Prospective	Patients with post-anoxic encephalopathy due to CA who were consecutively admitted to the ICU of Ticino Cardiocentre.	Not specified	NSE, NF-L	Survival	1 month after CA	14

[10]Daubin *et al.,* (2011). *BMC Cardiovasc Discord*. 11:48.
[11]Derwall *et al.,* (2009). *Crit Care*. 13(2):R58.
[12]Deye *et al.,* (2020). *Resuscitation*. 156:251-259.
[13]Disanto *et al.,* (2019). *Epilepsy Behav*. 101(Pt B):106432

Duez et al. 2018[14] PMID: 29175384	Retrospective	OHCA with a presumed cardiac origin, Glasgow Coma Scale below 8, sustained spontaneous circulation after resuscitation (no need for cardiac compressions for 20 min and clinical signs of circulation), aged between 18 and 80 years	Time to ROSC > 60 min, terminal disease, severe coagulopathy, unwitnessed OHCA with asystole as first rhythm, time from cardiac arrest to the initiation of cooling > 240 min, pregnancy, previous neurological disease with cognitive impairment, persistent cardiogenic shock, systolic blood pressure below 80 mmHg despite vasoactive treatment and/or aortic balloon pump intervention, suspected or confirmed acute intracerebral bleeding/acute stroke, acute coronary artery bypass surgery, or lack of consent	NSE, S100B	CPC 1&2 vs. 3-5	6 months post discharge	115
Ebner et al. 2020[15] PMID: 32445783	Prospective	Patients 18 years or older who were unconscious (GCS <8) on admission to hospital after out-of-hospital cardiac arrest of presumed cardiac cause, irrespective of the initial rhythm. Eligible patients had more than 20 consecutive minutes of ROSC.	Not Specified	GFAP, UCH-L1	CPC 1&2 vs. 3-5	6 months post arrest	717

[14]Duez *et al.,* (2018). *Resuscitation*. 122:79-86.
[15]Ebner *et al.,* (2020). *Resuscitation*. 154:61-68.

Einav et al. 2012[16] PMID: 22813607	Prospective	All patients with non-traumatic OHCA, age 18 years, who were brought after ROSC to the Shaare Zedek Medical Center	Arrest triggered by acute hemorrhage, hanging or drowning	NSE, S100B	CPC 1&2 vs. 3-5	Within 24hr of discharge	195
Einav et al. 2013[17] PMID: 23391666	Prospective	All patients aged ≥18 years who had undergone non-traumatic OHCA and resuscitation and were brought to the SZMC after ROSC	Patients who had arrested due to acute hemorrhage or external causes were excluded.	NSE, S100B	Survival	Hospital discharge	158
Elmer et al. 2016[18] PMID: 26457752	Prospective	In-hospital and out-of-hospital cardiac arrest; having received chest compressions or defibrillation; ED arrests considered OHCA	Younger than 18; presented greater than 6 hours after ROSC; had withdrawal of life-sustaining therapy within 6 hours of presentation, pregnant, prisoner, or they arrested secondary to a surgical or traumatic etiology	NSE, S100B	Survival	Hospital Discharge	86
Gillick et al. 2018[19] PMID: 29679695	Retrospective	Patients with OHCA admitted to the Intensive care unit	Not specified	NSE	CPC 1&2 vs. 3-5	At hospital discharge	72
Gulay et al. 2016[20] PMID: 27966313	Prospective	Not Specified	Age under 18, head trauma, trauma related arrest, status epilepticus, and patients who died in first 24 hours	NSE, S100B, GFAP	GOS 3-5 vs. 1&2	Discharge	30

[16]Einav *et al.,* (2012). *J Am Coll Cardiol*. 60(4):304-11.
[17]Einav *et al.,* (2013). *Resuscitation.* 84(8):1083-8
[18]Elmer *et al.,* (2016). *Crit Care Med*. 44(1):111-9.
[19]Gillick *et al.,* (2018). *Resuscitation*. 128:24-30.
[20]Gulay *et al.,* (2016). *Turk J Med Sci*. 46(5):1459-1468.

Hasper et al. 2009[21] PMID: 19874577	Retrospective	Not Specified	Death before 3rd day of study, incomplete data records, pre-existing need for renal replacement therapy, pre-existing advanced renal disease	NSE	CPC 1&2 vs. 3-5	ICU Discharge	171
Hasslacher et al. 2014[22] PMID: 25138227	Prospective	All consecutive adult patients (at least 18 years) admitted to the medical ICU after successful CPR.	Presence of neuroendocrine tumour, stroke, intracranial hemorrhage or trauma as a cause of CA or life expectancy of <24h as determined by the treating physicians.	NSE	CPC 1&2 vs. 3-5	At hospital discharge	134
Hasslacher et al. 2020[23] PMID: 32004662	Prospective	Adult patients aged ≥18 years with an in-hospital or out-of-hospital cardiac arrest with presumed cardiac cause admitted to the ICU after successful CPR	Presence of neuroendocrine tumour, stroke, intracranial hemorrhage or trauma as a cause of CA or life expectancy of <24h as determined by the treating physicians.	Tau	CPC 1&2 vs. 3-5	Discharge from hospital or at death in ICU	132
Hayashida et al. 2010[24] PMID: 20033352	Retrospective	Out of hospital cardiac arrest patients admitted to the emergency medical center	Patients with a history of trauma, extracorporeal CPR, severe stroke on initial head CT, withdrawal due to terminal disease or persistent untreatable hypotension	GFAP	CPC 1&2 vs. 3-5	6 months after ROSC	21

[21]Hasper *et al.,* (2009). *Crit Care*. 13(5):R168.
[22]Hasslacher *et al.,* (2014). *Intensive Care Med*. 40(10):1518-27.
[23]Hasslacher *et al.,* (2020). *Resuscitation*. 148:207-214.
[24]Hayashida *et al.,* (2010). *Neurocrit Care*. 12(2):252-7.

Helwig et al. 2017[25] PMID: 28054291	Prospective	A documented successful out of hospital or in-hospital CPR within the last 60 h	(1) age under 18 years, (2) previous stroke within the last 12 months, (3) traumatic brain injury within the last 12 months, (4) any brain tumor in medical history	NSE, GFAP	mGOS 0-3 vs. 4&5	4 weeks after CPR	100
Hoiland et al. 2021[26] PMID: 34287000	Prospective	Eligible patients met the following inclusion criteria: a) age ≥ 19; b) sustained cardiac arrest > 10 minutes requiring cardiopulmonary resuscitation; c) post-return of spontaneous circulation (ROSC) Glasgow Coma Score ≤ 8 and motor score ≤ 5 in the absence of clinical confounders (sedative medications, core body temperature < 35ºC, electrolyte disturbances, hypoglycemia); d) study enrollment with 72 hours of the initial cardiac arrest.	Patients were excluded if they met any of the following: a) anticipated withdrawal of life-sustaining therapies within the next 24 hours; b) previous or current traumatic brain injury, intracranial hemorrhage or stroke; c) concurrent coagulopathy (international normalized ratio > 1.5, prothrombin time > 40 seconds, platelet count < 100 x 10^9 cells); d) concurrent anti-platelet or anticoagulant medications; e) anticipated cardiac catheterization within the next 7 days.	NSE, GFAP, Nf-L, Tau, UCH-L1	CPC 1&2 vs. 3-5	6 months post arrest	18

[25]Helwig *et al.,* (2017). *Neurocrit Care*. 27(1):68-74.
[26]Hoiland *et al.,* (2021). *Circ Res*. 129(5):583-597.

Huang et al. 2016[27] PMID: 27256246	Prospective	Eligible patients included adult (> 18 years old) non-traumatic OHCA patients who were successfully resuscitated with sustained ROSC for more than 20 minutes	Patients were excluded if they were transferred to other hospitals for post-cardiac arrest care, or if their relatives or surrogates refused to participate in the study. Patients with do not attempt resuscitation orders and those expecting to survive for less than 180 days due to underlying diseases before the cardiac arrest also were excluded	S100B	Survival	Hospital discharge	99
Huesgen et al. 2021[28] PMID: 34223394	Prospective	Non-traumatic OHCA patients	Patients were excluded if pregnant, incarcerated, or had advanced directives precluding resuscitation. Other exclusion criteria were the presence of another neurologic disease, brain injury, brain cancer, end-stage renal disease, and end-stage liver disease.	GFAP, Nf-L, UCH-L1, Tau, & S100B	CPC 1&2 vs. CPC 3-5	6 months post arrest	22
Hunziker et al. 2021[29] PMID: 33472689	Prospective	OHCA patients	None	NSE & Nf-L	CPC 1&2 vs. CPC 3-5	Hospital discharge	164
Jakkula et al. 2019[30] PMID: 31088512	Retrospective	Not Specified	Not Specified	NSE	CPC 1&2 vs. 3-5	6 months post arrest	118

[27]Huang *et al.,* (2016). *Sci Rep*. 6:27187.
[28]Huesgen *et al.,* (2021). *Resusc Plus*. 7:100133.
[29]Hunziker *et al.,* (2021). *Crit Care*. 25(1):32.
[30]Jakkula *et al.,* (2019). *Crit Care*. 23(1):171.

Jang et al. 2019[31] PMID: 30732223	Prospective	Adult patients (aged >18 years) who were successfully resuscitated and achieved ROSC after non-traumatic out of hospital CA (OHCA) and then received TTM at 33°C were enrolled in this study	Patients with possible causes of coma other than CA (head injury, poisoning, or cerebrovascular accident) and those with severe neurological disorder or stroke, end-stage non-cardiac disease, severe disability (Glasgow-Pittsburgh cerebral performance category, CPC ≥3), or end-stage renal or liver disease were excluded. In addition, patients who died within 24hours after hospital admission were not included.	S100B	CPC 1&2 vs. 3-5	3 months post CA	97
Kaneko et al. 2017[32] PMID: 28482803	Prospective	Not Specified	Trauma, non-cardiogenic disorder	NSE, S100B	CPC 1&2 vs. 3-5	Hospital discharge	43
Kang et al. 2021[33] PMID: 33917473	Prospective	Adult comatose OHCA patients treated with TT<.	Next of kin declined treatment following cardiac arrest, <18 years of age, if the cardiac arrest was cause due to trauma, failure to maintain TTM, ineligibility for lumbar puncture	NSE, S100B	CPC 1&2 vs. CPC 3-5	3 months after ROSC	45

[31]Jang *et al.,* (2019). *Medicine (Baltimore)*. 98(6):e14496.
[32]Kaneko *et al.,* (2017). *BMC Cardiovasc Disord*. 17(1):111.
[33]Kang *et al.,* (2021). *J Clin Med*. 10(7):1531.

Kim et al. 2012[34] PMID: 22932993	Retrospective	OHCA patients older than 15 years who were treated with mild hypothermia and underwent a brain MRI for prognostic purposes were identified	Not Specified	NSE	CPC 1&2 vs. 3-5	6 months post arrest	43
Kim et al. 2020[35] PMID: 33002033	Retrospective	Patients who underwent at least one NSE value measurement between 48 and 72 hours after ROC and received both a brain CT scan within 24 hour after ROSC and DW-MRI within 7 days after ROSC	Age <18years old, CA due to trauma or intracranial hemorrhage, a previous history of neurological disease and CT or DW-MRI with a poor image quality	NSE	CPC 1&2 vs. 3-5	6 months after CA	109
Larsson et al. 2014[36] PMID: 25260722	Prospective	Inclusion criteria were CA treated with TH and age > 18 years.	Not specified	NSE, S100B, GFAP	CPC 1&2 vs. 3-5	6 months post arrest	125

[34]Kim *et al.,* (2012). *Neurocrit Care*. 17(3):412-20.
[35]Kim *eta l.,* (2020). *PLoS One.* 15(10):e0239979.
[36]Larsson *et al.,* (2014). *Resuscitation*. 85(12):1654-61.

Lascarrou et al. 2021[37] PMID: 33301887	Prospective	Patients resuscitated after cardiac arrest in a non-shockable rhythm due to any cause, ≥18 years of age	Exclusion criteria were a no-flow time > 10 minutes; a low-flow time (from initiation of CPR to ROSC) of more than 60 minutes; major hemodynamic instability (continuous epinephrine or norepinephrine infusion >1 µg//Kg/min); time from cardiac arrest to screening of more than 300 minutes; moribund condition; Child–Pugh class C cirrhosis of the liver; pregnancy or breast-feeding; status of being under guardianship; status of being an inmate at a correctional facility; previous inclusion in another randomized, controlled trial involving patients with cardiac arrest in which the neurologic outcome at 90 days was assessed as the primary end point; lack of health insurance; and decision by the next of kin for the patient not to participate.	NSE	CPC 1&2 vs. CPC 3-5	90 days post arrest	101

[37]Lascarrou *et al.,* (2021). *Resuscitation*. 158:193-200.

Leao et al. 2015[38] PMID: 26761469	Prospective	Systolic BP >80, GCS <9,	Patients with a core temperature lower than 30°C, coagulopathy, cryoglobulinemia, severe bleeding, intracerebral hemorrhage and known terminal illness were excluded.	NSE	CPC 1&2 vs. 3-5	6 months (not specified if post d/c or arrest)	67
Lee et al. 2020[39] PMID: 31187435	Retrospective	Non-traumatic comatose cardiac arrest survivors >18years old who were treated with TH and for whom HbA1c was measured.	Transferred to another facility or died during TH, no measurement of HbA1c, treated with a target temperature other than 33 degrees Celsius and/or target duration other than 24h, received ECMO during post-cardiac arrest care or missing data regarding glucose levels during TH.	NSE	CPC 1&2 vs. 3-5	6 months after CA	384

[38]Leao *et al.,* (2015). *Rev Bras Ter Intensiva*. 27(4):322-32.
[39]Lee *et al.,* (2020). *Neurocrit Care*. 32(2):448-458.

Lee et al. 2021[40] PMID: 34302037	Retrospective	OHCA patients >18 years of age	Confirmation of hemorrhagic or ischemic stroke as the cause of cardiac arrest, CPC of 3 or 4 before cardiac arrest, body temperature <30 °C upon arrival, non-provision of post-resuscitation care, including TTM, meaningful response to verbal commands following ROSC, non-measurement of serum NSE level at 48 or 72 h afer ROSC, non-assessment of FOUR score or GCS score afer ROSC, initial GCS score>8, WLST, and unknown neurological outcome at 6 months.	NSE	CPC 1&2 vs. CPC 3-5	6 months post-cardiac arrest	475

[40]Lee *et al.,* (2021). *Sci Rep*. 11(1):15607

Martens et al. 1996[41] PMID: 8808372	Prospective	Patients who sustained cardiac arrest (out of hospital or in hospital) who did not wake up shortly after ROSC.	Patients dying due to cardiac failure before level of consciousness could be adequately assessed.	NSE	Survival	At discharge from ICU	34
Martinez-Losas et al. 2020[42] PMID: 30857978	Retrospective	In and out of hospital CA survivors of suspected cardiac origin, irrespective of initial rhythm and cooled to 32 degrees to 34 degrees for 24 hours, confirmation of both persistent comatose state after ROSC and absence of contraindications for TTM, and had at least 1 serum NSE determination during hospitalization and did not die within 72 hours after admission.	Not specified	NSE	CPC 1&2 vs. 3-5	3 months after CA	320

[41]Martens (1996). *Acad Emerg Med*. 3(2):126-31.
[42]Martinez-Losas *et al.,* (2020). *Rev Esp Cardiol (Engl Ed)*. 73(2):123-130.

Mattsson et al. 2017[43] PMID: 28981963	Prospective	The TTM trial was a prospective study of effects of targeted temperature management at 33C versus 36C in patients who were unconscious after out-of-hospital cardiac arrest.	Not specified	NSE, Tau (NSE not included in analyses to avoid duplication)	CPC 1&2 vs. 3-5	6 months post CA	689
Meisner et al. 2020[44] PMID: 30397762	Retrospective	Patients successfully resuscitated from non-traumatic cardiac arrest outside of the hospital.	Patients who died within 8 hours, with missing information on the temperature profile or who were under 18 years of age.	NSE	GOS 3-5 vs. 1&2	Time of transfer out of the ICU	149
Mortberg et al. 2011[45] PMID: 22092212	Prospective	Patients resuscitated from CA of age >18 years, systolic pressure >80mmHg for more than 5 min after ROSC and unconscious with GCS <7 and included within 6h after CA.	Patients with terminal disease.	Tau	CPC 1&2 vs. 3-5	At discharge and 6 months after CA. The higher of the 2 CPC scores were used for patients who died after ICU discharge.	22

[43]Mattsson *et al.,* (2017). *Ann Neurol*. 82(5):665-675.
[44]Meisner *et al.,* (2020). *Med Klin Intensivmed Notfmed*. 115(1):43-51.
[45]Mortberg *et al.,* (2011). *Acta Anaesthesiol Scand*. 55(9):1132-8.

Moseby-Knappe et al. 2019[46] PMID: 30383090	Prospective	Patients 18 years or older who were unconscious (GCS <8) on admission to hospital after out-of-hospital cardiac arrest of presumed cardiac cause, irrespective of the initial rhythm. Eligible patients had more than 20 consecutive minutes of ROSC.	Interval from the return of spontaneous circulation to screening of more than 240 minutes, unwitnessed arrest with asystole as the initial rhythm, suspected or known acute intracranial hemorrhage or stroke and a body temperature of <30 degrees Celcius.	NSE, S100B, NF-L, Tau (NSE not included in analyses to avoid duplication)	CPC 1&2 vs. 3-5	6 months after CA	717
Moseby-Knappe et al. 2021[47] PMID: 34417831	Retrospective	Patients 18 years of age or older who were unconscious (GCS <8) on admission to the hospital after out-of-hospital cardiac arrest of presumed cardiac cause, irrespective of the initial rhythm. More than 20 consecutive minutes of spontaneous circulation after resuscitation.	An interval from the return of spontaneous circulation to screening of more than 240 minutes, unwitnessed arrest with asystole as the initial rhythm, suspected or known acute intracranial hemorrhage or stroke, and a body temperature of less than 30°C.	NSE, S100B, Nf-L, Tau, UCH-L1, GFAP	CPC 1&2 vs. CPC 3-5	6 months post-cardiac arrest	717

[46]Moseby-Knappe *et al.,* (2019). *JAMA Neurol*. 76(1):64-71.
[47]Moseby-Knappe *et al.,* (2021). *Intensive Care Med*. 47(9):984-994.

Nakstad et al. 2020[48] PMID: 31926258	Prospective	Patients ≥18 years old, comatose (GCS<9) OHCA patients of cardiac and non-cardiac causes with stable ROSC (>20min).	OHCA following trauma/acute onset intra-cerebral pathology, CPR<5min followed by spontaneous awakening, OUHU admission >6h after OHCA and treatment withdrawal in the ED (based on an abstain-from-resuscitation wish, terminal cancer disease, or very advanced age/dementia).	NSE	CPC 1&2 vs. 3-5	6 months after OHCA	259
Okasanen et al. 2009[49] PMID: 18954930	Retrospective	Out-of-hospital VF of presumed cardiac origin, witnessed arrest, age ≥18 years, basic life support delayed less than 15min, ROSC less than 35 min and unresponsiveness at hospital admission	Persistent hypotension (MAP <65mmHg for >30min) despite therapy, pregnancy, terminal illness, pre-arrest illness limiting follow-up (e.g.. Dementia) or DNR order.	NSE	CPC 1&2 vs. 3-5	6 months after CA	90
Peluso et al. 2021[50] PMID: 34356123	Retrospective	Adult patients (>18 years) who remained with a Glasgow coma scale (GCS) <9 after hospital admission and were admitted into the intensive care unit (ICU).	Patients with early deaths or awakening (<24 h) who did not have at least two prognostic tools assessed.	NSE	CPC 1&2 vs. CPC 3-5	3 months after CA	137

[48]Nakstad *et al.,* (2020). *Resuscitation*. 149:170-179.
[49]Oksanen *et al.,* (2009). *Resuscitation*. 80(2):165-70.
[50]Peluso *et al.,* (2021). *Brain Sci*. 11(7):888.

Pfeifer et al. 2005[51] PMID: 15797275	Prospective	Patients who arrived at our ICU within 12hours after ROSC and survived for a minimum of 48h	Not specified	NSE, S100B	GOS 3-5 vs. 1&2	28 days after CPR	97
Prohl et al. 2007[52] PMID: 17414735	Prospective	Glasgow Coma scale ≤3	Patients were excluded if the observed interval between collapse and the start of cardiopulmonary resuscitation had lasted for >15 mins. Excluded in ROSC could not be achieved in 60minutes. Patients with previous cardiac arrest and with known or co-existing neurologic disorders or neoplasms of the amine precursor uptake and decarboxylation system were excluded.	NSE, S100B	CPC 1-3 vs. 4&5	6-months post arrest	80
Rana et al. 2012[53] PMID: 22322567	Prospective	Witnessed out of hospital CA of presumed cardiac origin	Presence of previous neurological disease or pregnancy	NSE, S100B	GOS 3-5 vs. 1&2; mGOS 3-5 vs. 1&2	6 months after CA	97
Rana et al. 2013[54] PMID: 23287695	Prospective	Age 18-80 years old, witnessed out of hospital CA of presumed cardiac origin, absence of previous neurological disease and pregnancy	Not specified	NF-L	mGOS 3-5 vs. 1&2	6 months after CPR	61

[51]Pfeifer *et al.,* (2005). *Resuscitation*. 65(1):49-55.
[52]Prohl *et al.,* (2007). *Crit Care Med*. 35(5):1230-7.
[53]Rana *et al.,* (2012). *Clin Res Cardiol*. 101(7):533-43
[54]Rana *et al.,* (2013). *Int J Cardiol*. 168(2):1322-7

Roger et al. 2015[55] PMID: 26324761	Retrospective	Our inclusion criteria included adult patients (18 years) successfully resuscitated following OHCA and admitted to ICUs	In-hospital cardiac arrest patients and patients who died before ICU admission were excluded	NSE	CPC 1&2 vs. 3-5	6 months post CA	80
Rosen et al. 2001[56] PMID: 11382525	Prospective	Patients with OHCA	Patients with a fatal outcome within 24 h were not included in the study. (17 patients with cardiac arrests were not included for technical reasons.)	NSE, S100B	GOS 3-5 vs. 1&2	Days 14, 45, 90 and 365 post arrest - used the best recorded result at any of the examinations	65
Rossetti et al. 2012[57] PMID: 22323758	Prospective	Consecutive comatose adults admitted between December 2009 and April 2011 to the Department of Intensive Care Medicine of our hospital, after successful resuscitation from CA, and treated with TH	Patients diagnosed as being in brain death upon rewarming, or without signs of EEG activity ("flat recording"), were not included in the study	NSE	CPC 1&2 vs. 3-5	3 months from discharge	61
Ruivo et al. 2016[58] PMID: 27374413	Retrospective	Comatose adults (unable to follow verbal commands after ROSC) aged ≥18 years admitted to the ICU with ROSC after in-hospital or out-of-hospital CA who were treated by TH	Patients without known time of CA, in a comatose state before CA, or with a terminal illness that preceded CA were excluded	NSE	CPC 1&2 vs. 3-5	6 months post discharge	15

[55]Roger *et al.,* (2015). *Anaesth Crit Care Pain Med*. 34(4):231-7.
[56]Rosen *et al.,* (2001). *Resuscitation*. 49(2):183-91.
[57]Rossetti *et al.,* (2012). *Neurology*. 78(111):796-802.
[58]Ruivo *et al.,* (2016). *Rev Port Cardiol*. 35(7-8):423-31.

Ryczek et al. 2021[59] PMID: 34125928	Prospective	OHCA patients who remained unconscious at first presentation with a Glasgow Coma Scale score ≤8.	Not specified	NSE	CPC 1&2 vs. CPC 3-5	Discharge (ICU or hospital discharge not specified)	82
Ryoo et al. 2020[60] PMID: 31936049	Retrospective	Age >18 years; OHCA; unconsciousness after ROSC; treated with TTM	Intracranial hemorrhage, acute stroke, DNR, pre-arrest cerebral dysfunction, severe comorbidity and expected death within 180 days	NSE	CPC 1&2 vs. 3-5	28 days after cardiac arrest	160
Samaniego et al. 2011[61] PMID: 20680517	Prospective	Age 18 years or older, successful cardiopulmonary resuscitation and persistent coma defined as: no eye opening to voice and inability to follow commands	Pre-existing ‘‘do not resuscitate’’ status, severe coexisting systemic disease with a limited life expectancy, and brain death, patients who died within 72h of initial cardiac arrest.	NSE	GOS 3-5 vs. 1&2	3 months post arrest	85

[59]Ryczek *et al.,*(2021). *Kardiol Pol*. 79(5):546-553.
[60]Ryoo *et al.,* (2020). *J Clin Med*. 9(1):159.
[61]Samaniego *et al.,* (2011). *Neurocrit Care*. 15(1):113-9.

Scheel et al. 2013[62] PMID: 23566292	Retrospective	Cranial CT within first seven days following cardiac arrest	Thirteen patients were excluded from further analysis for findings that would have biased measurement of Hounsfield units and GWR calculation (only contrast enhanced CCT available (3), hydrocephalus and shunt artifact (3), severe movement artifacts (2), intracerebral hemorrhage (3), old large ischemic lesion (1), massive calcification of the basal ganglia (1)	NSE	CPC 1&2 vs. 3-5	ICU Discharge	98
Schoerkhuber et al. 1999[63] PMID: 10436107	Prospective	Adult patients aged 18-75 years admitted after witnessed, non traumatic, normothermic, in- or out of hospital cardiac arrest	No ROSC could be achieved or if spontaneous circulation returned within the first minute of collapse	NSE	CPC 1&2 vs. 3-5	Best CPC within 6 months after ROSC	56

[62]Scheel *et al.,* (2013). *Scand J Trauma Resusc Emerg Med*. 21:23.
[63]Schoerkhuber *et al.,* (1999). *Stroke*. 30(8):1598-603.

Schrage et al. 2019[64] PMID: 30654013	Retrospective	Patients admitted for ECMO treatment of cardiogenic shock or refractory cardiac arrest and prior CPR. Only patients with ECMO implantation within 6h after CPR or ECMO implantation during active CPR and with available NSE were selected.	Patients who were awake within 24h after the index event and patients who decreased within 24h after the index event	NSE	CPC 1-3 vs. 4&5	Hospital discharge	129

[64]Schrage *et al.,* (2019). *Resuscitation*. 136:14-20.

Shinozaki et al. 2009[65] PMID: 19535196	Prospective	All patients presented with either out-of-hospital or in-hospital non-traumatic CA were included if they met the definition for "survived event" who remained unconscious (GCS≤8) and age ≥18 years. "Survived event" in the out-of-hospital setting indicates sustained spontaneous circulation following ROSC until admission and transfer of care to the medical staff at the receiving hospital. In the in-hospital setting, "survived event" means sustained circulation following ROSC for >20min.	Death before admission or within 20 min after ROSC, age under 17 years, previously known irreversible brain damage (CPC 3-4 before CA event), recovery of consciousness (GCS≥9) soon after ROSC until admission, patients whose CPC were not evaluated due to death under analgesic sedation.	NSE, S100B	CPC 1&2 vs. 3-5	Best-ever achieved CPC within 6 months from the onset of CA in cases "discharged alive" and best-ever achieved CPC for the time period between onset of CA and in-hospital death in cases "discharged dead." In cases of "discharged dead within 24h after CA," the patients who had no consciousness were classified into "poor neurological outcome."	80

[65]Shinozaki *et al.,* (2009). *Resuscitation*. 80(8):870-5.

Son et al. 2020[66] PMID: 32164225	Retrospective	Adult comatose out-of-hospital cardiac arrest survivors treated with TTM, patients with collected NSE levels who underwent brain imaging (CT, MRI or both) after ROSC	Patients aged <18 years, patients with traumatic CA, patients with an interrupted TTM, patients not eligible for TTM, patients administered extracorporeal membrane oxygenation and patients ineligible for lumbar puncture.	NSE	CPC 1&2 vs. 3-5	3 months after CA	58
Song et al. 2010[67] PMID: 20047785	Prospective	Patients who presented with CA	Gained ROSC before arriving to ED, did not receive CPR due to DNR order, were regarded as dead on arrival or were pregnant	S100B	Survival	1 month after CA	151
Song et al. 2021[68] PMID: 33922191	Retrospective	Non-traumatic comatose OHCA adult survivors >18 years of age and treated with TTM	Ineligible for TTM, who failed to maintain a temperature of 33◦C during TTM due to unstable hemodynamics, whose TTM initiation was performed 6 h after ROSC, who had insufficient laboratory data obtained <6 h after ROSC, or those who had missing information at the time of CA or CPR.	NSE	CPC 1&2 vs. CPC 3-5	3 months after ROSC	106
Stammet et al. 2013[69] PMID: 23684684	Prospective	Unconscious on admission, GCS <8	Not Specified	NSE, S100B	CPC 1&2 vs. 3-5	6 months (not specified if post arrest or post d/c)	75

[66]Son *et al.,* (2020). *J Clin Med*. 9(3):744.
[67]Song *et al.,* (2010). *Resuscitation*. 81(3):337-42.
[68]Song *et al.,* (2021). *J Clin Med*. 10(9):1825.
[69]Stammet *et al.,* (2013). *J Am Coll Cardiol*. 62(9):851-8.

Stammet et al. 2015[70] PMID: 25975474	Prospective	Patients 18 years or older who were unconscious (GCS <8) on admission to hospital after out-of-hospital cardiac arrest of presumed cardiac cause, irrespective of the initial rhythm. Eligible patients had more than 20 consecutive minutes of ROSC.	Interval from the return of spontaneous circulation to screening of more than 240 minutes, unwitnessed arrest with asystole as the initial rhythm, suspected or known acute intracranial hemorrhage or stroke and a body temperature of <30 degrees Celsius.	NSE	CPC 1&2 vs. 3-5	6 months after CA	686
Stammet et al. 2017[71] PMID: 28629472	Prospective	Patients 18 years or older who were unconscious (GCS <8) on admission to hospital after out-of-hospital cardiac arrest of presumed cardiac cause, irrespective of the initial rhythm. Eligible patients had more than 20 consecutive minutes of ROSC.	Not Specified	S100B	CPC 1&2 vs. 3-5	6 months (not specified if post arrest or post d/c)	687

[70]Stammet *et al.,* (2015). *J Am Coll Cardiol*. 65(19):2104-14.
[71]Stammet *et al.,* (2017). *Crit Care*. 21(1):153.

Stefanizzi et al. 2020[72] PMID: 32575355	Retrospective	25 cardiac arrest patients with either a good (CPC 1) or poor (CPC 5) neurological outcome at 6 months were enrolled in this study.	Not specified	NSE	CPC 1 vs. 5	Six months (post-CA or discharge not specified)	50
Steffen et al. 2010[73] PMID: 20403168	Retrospective	Not Specified	Not Specified	NSE	CPC 1&2 vs. 3-5	ICU discharge	230
Storm et al. 2012[74] PMID: 22284447	Prospective	Thirty-five consecutive patients resuscitated from cardiac arrest were included in the study.	Not specified	NSE	CPC 1&2 vs. 3-5	Discharge from ICU	35
Streitberger et al. 2017[75] PMID: 28426467	Retrospective	Shockable or non-shockable rhythm, TTM,	Not Specified	NSE	CPC 1&2 vs. 3-5	At ICU discharge	1053
Sugita et al. 2017[76] PMID: 28950909	Prospective	Patients who achieved ROSC from OHCA and who were brought to the emergency and critical care department, regardless of cardiac or non-cardiac etiology.	Informed consent not obtained, cases of multiple trauma, end stage malignancy, death in the ED, bedridden prior to hospitalization and <18 years old.	NSE	CPC 1&2 vs. 3-5	90 days after ROSC	128

[72]Stefanizzi *et al.,* (2020). *Int J Mol Sci*. 21(12):4353.
[73]Steffen *et al.,* (2010). *Crit Care*. 14(2):R69.
[74]Storm *et al.,* (2012). *Scand J Trauma Resusc Emerg Med*. 20:6.
[75]Streitberger *et al.,* (2017). *Crit Care Med*. 45(7):1145-1151.
[76]Sugita *et al.,* (2017). *Crit Care*. 21(1):247.

Tat et al. 2019[77] PMID: 30650128	Prospective	Between ages of 18-85 and cardiac arrest	Age under 18 or over 85, pregnancy, trauma, acute bleeding from non-traumatic condition, re-arrest with unsuccessful resuscitation within 6 hours of hospital arrival, arrest secondary to hypothermia, terminal neoplastic disease, inmates, and absence of informed consent.	NSE, S100B	Survival	30 days post arrest	40

[77]Tat- *et al.,* (2019). *PLoS One*. 14(1):e0210666.

Tiainen et al. 2003[78] PMID: 14631087	Prospective	All adult patients aged 18-75 years of age, witnessed out of hospital CA, ventricular fibrillation or non-perfusing tachycardia as initial rhythm, presumed cardiac origin of arrest, estimated interval of 5-15min from collapse to first attempt at resuscitation by emergency medical personnel and an interval of <60minutes from collapse to ROSC.	Presence of emergency medical personnel, CA from intoxication or trauma, response to verbal command after ROSC and before randomization, tympanic temperate <30 degrees celsius on admission, evidence of hypotension (MAP <60mmHg) for >30min after ROSC and before randomization, evidence of hypoxia (arterial O2 sat <85%) for >15 minutes after ROSC and before randomization, a terminal illness, pre-existing coagulopathy, pregnancy, unavailable for follow-up, enrollment in another study.	NSE, S100B	CPC 1&2 vs. 3-5	6 months after CA	70
Tsetsou et al. 2018[79] PMID: 28337603	Prospective	Patients older than 18 years successfully resuscitated after CA (in-hospital: out-of-hospital CA ratio was 1:10), who were managed with TTM at 36degrees C in the medical-surgical intensive care unit	Patients that died within 24 h after CA were excluded	NSE	CPC 1&2 vs. 3-5	3 months from discharge	61

[78]Tiainen *et al.,* (2003). *Stroke*. 34(12):2881-2886
[79]Tsetsou *et al.,* (2018). *Neurocrit Care*. 28(1):104-109

Wihersaari et al. 2019[80] PMID: 31022497	Prospective	OHCA patients who were unconscious and admitted to Finnish ICU, those with biomarkers	Not Specified	NSE	CPC 1&2 vs. 3-5	12 months post arrest	249
Wihersaari et al. 2021[81] PMID: 32852582	Prospective	120 comatose OHCA patients resuscitated from an initial shockable rhythm	Not Specified	NF-L	CPC 1&2 vs. 3-5	6 months after CA	112
Wurm et al., 2021[82] PMID: 34342833	Retrospective	Patients were included with a Glasgow Coma Scale score of 3 at admission and when the reason for cardiac arrest was either cardiac, respiratory, hemodynamic, or metabolic.	Patients were excluded when there was a history of previous cardiac arrest, neurological disorders or central nervous system neoplasms, psychiatric illness, substance abuse including alcohol, and the ongoing use of psychotropic medications.	NSE, S100B, Nf-L	CPC 1&2 vs. CPC 3-5	6 months following cardiac arrest	70
You et al. 2019[83] PMID: 31585184	Prospective	OHCA patients >18 years old who had been treated using TTM	Patients with traumatic cardiac arrest, patients ineligible for lumbar puncture (ie. Brain CT showed severe cerebral edema, obliteration of the basal cisterns or an occult intracranial mass lesion), patients receiving ECMO, relatives unable to consent to an LP	NSE	CPC 1&2 vs. 3-5	6 months after ROSC	34

[80] Wihersaari *et al.,* (2019). *Resuscitation*. 139:214-221.
[81] Wihersaari *et al.,* (2021). *Intensiv Care Med*. 47(1):39-48.
[82] Wurm *et al.,* (2021). *Neurocrit Care*. Doi: 10.1007/s12028-021-01321-1
[83] You *et al.,* (2019). *Resuscitation*. 145:185-191.

Zellner et al. 2013[84] PMID: 23528678	Retrospective	Coma after cardiac arrest with ROSC. Patients needed to be 18 years or older. Furthermore the decision to apply TH needed to be made by the attending physician. The patients also needed to survive the first night in the ICU	Patients with do-not-resuscitate/-do-not-intubate orders after initial cardiopulmonary resuscitation(CPR) and patients with in-hospital cardiac arrests in the operating room, the catheterization lab, on an ICU or with telemetry.	NSE, S100B	CPC 1&2 vs. 3-5	6 months post discharge	123
Zhai et al. 2020[85] PMID: 32802436	Retrospective	All emergency department OHCA patients who achieved ROSC.	Pre-arrest cognitive impairment, existing terminal illness, missing data regarding baseline characteristics, or outcome	NSE	Survival	Hospital discharge	61
Zingler et al. 2003[86] PMID: 12584414	Prospective	Not Specified	Hypothermia (<35C)	NSE, S100B	CPC 1-3 vs. 4&5	12 weeks post arrest	27

[84]Zellner *et al.,* (2013). *Resuscitation*. 84(10):1382-6.
[85]Zhai *et al.,* (2020). *J Thorac Dis*. 12(7):3573-3581.
[86]Zingler *et al.,* (2003). *Eur Neurol*. 49(2):79-84.

eTable 2. Receiver Operator Characteristic Curve Analysis for the Diagnostic Accuracy of Brain Biomarkers for Predicting Unfavorable outcome at 48 hours in patients where outcome was determined ≥3 months following cardiac arrest.

	AUC	95% CI's
NSE	0.83	0.75 – 0.89
S100B	0.85	0.76 – 0.90
GFAP	0.81	0.46 – 0.96
Nf-L	0.92	0.88 – 0.95
Tau	0.86	0.73 – 0.93
UCH-L1	0.88	0.52 – 0.99

eTable 3. Concentration thresholds for each biomarker. Concentration threshold and corresponding sensitivity to achieve 95% & 100% specificity for each biomarker. Values are derived from the SROCs presented in the main analysis (Figure 2).

Biomarker	Specificity Cut-Off	Sensitivity	Concentration Threshold (ug/L or pg/mL)
NSE	95%	55%	46.7
	100%	6%	455
S100B	95%	56%	0.287
	100%	5%	5.95
GFAP	95%	52%	287
	100%	11%	33392
NF-L	95%	78%	553
	100%	21%	44766
Tau	95%	64%	91.5
	100%	2.9%	8176
UCH-L1	95%	64%	583
	100%	6%	11644

eTable 4. Studies including outcome determination at times other than hospital discharge and 6-months.

Study	Outcome determination	Sample size
Barbella et al. 2020; PMID: 32044334	3 months post CA	158
Bongiovanni et al. 2020; PMID: 32016534	3 months after CA	485
Bottiger et al. 2001; PMID: 11390339	14 days post ROSC	66
Clifford-Mobley et al. 2020; PMID: 31615270	ICU discharge	142
Daubin et al. 2011; PMID: 21824428	3 months post CA	97
Derwall et al. 2009; PMID: 19368739	14 days post ROSC	68
Deye et al. 2020; PMID: 32858156	At hospital discharge and 3 months after CA	330
Disanto et al. 2019; PMID: 31375414	1 month after CA	14
Einav et al. 2012; PMID: 22813607	Within 24hr of discharge	195
Hasper et al. 2009; PMID: 19874577	ICU Discharge	171
Helwig et al. 2017; PMID: 28054291	4 weeks after CPR	100
Jang et al. 2019; PMID: 30732223	3 months post CA	97
Kang et al. 2021; PMID: 33917473	3 months after ROSC	45
Lascarrou et al. 2021; PMID: 33301887	90 days post arrest	101
Martens et al. 1996; PMID: 8808372	At discharge from ICU	34
Martinez-Losas et al. 2020; PMID: 30857978	3 months after CA	320
Meisner et al. 2020; PMID: 30397762	Time of transfer out of the ICU	149
Peluso et al. 2021; PMID: 34356123	3 months after CA	137
Pfeifer et al. 200; PMID: 15797275	28 days after CPR	97
Rosen et al. 2001; PMID: 11382525	Days 14, 45, 90 and 365 post arrest	65
Rossetti et al. 2012; PMID: 22323758	3 months from discharge	61
Ryczek et al. 2021; PMID: 34125928	Discharge (ICU or hospital discharge not specified)	82
Ryoo et al. 2020; PMID: 31936049	28 days after cardiac arrest	160
Samaniego et al. 2011; PMID: 20680517	3 months post arrest	85
Scheel et al. 2013; PMID: 23566292	ICU Discharge	98
Son et al. 2020; PMID: 32164225	3 months after CA	58
Song et al. 2010; PMID: 20047785	1 month after CA	151
Song et al. 2021; PMID: 33922191	3 months after ROSC	106
Steffen et al. 2010; PMID: 20403168	ICU discharge	230
Storm et al. 2012; PMID: 22284447	Discharge from ICU	35
Streitberger et al. 2017; PMID: 28426467	At ICU discharge	1053
Sugita et al. 2017; PMID: 28426467	90 days after ROSC	128
Tat et al. 2019; PMID: 30650128	30 days post arrest	40
Tsetsou et al. 2018; PMID: 28337603	3 months from discharge	61
Wihersaari et al. 2019; PMID: 31022497	12 months post arrest	249
Zingler et al. 2003; PMID: 12584414	12 weeks post arrest	27
36 studies (41.9% of total)		**5495 patients (52.0% of total)**

CA, Cardiac arrest; CPR, cardiopulmonary resuscitation; ICU, Intensive care unit; ROSC, return of spontaneous circulation

eTable 5. Studies including survival versus death as an outcome.

Study	Sample size
Auer et al. 2006; PMID: 17175624	17
Clifford-Mobley et al. 2020; PMID: 31615270	142
Disanto et al. 2019; PMID: 31375414	14
Einav et al. 2013; PMID: 23391666	158
Elmer et al. 2016; PMID: 26457752	86
Huang et al. 2016; PMID: 27256246	99
Martens et al. 1996; PMID: 8808372	34
Song et al. 2010; PMID: 20047785	151
Tat et al. 2019; PMID: 30650128	40
Zhai et al. PMID: 32802436	61
10 studies (11.6% of total)	**802 patients (7.6% of total)**

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