ONLINE FIRST

CARDIOLOGY JOURNAL

ISSN: 1897-5593

e-ISSN: 1898-018X

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DOI: 10.5603/cj.103883

Article type: Original Article

Submitted: 2024-12-03

Accepted: 2025-01-22

Published online: 2025-03-10

Articles in "Cardiology Journal" are listed in PubMed.

ORIGINAL ARTICLE

DOI:10.5603/cj.103883

Submitted: 3.12.2024

Accepted: 22.01.2025

The utility of brain biomarkers in predicting survival and neurological outcomes in pediatric patients after cardiac arrest: A systematic review and meta-analysis

Running head: **Brain biomarkers in pediatric cardiac arrest**

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ABSTRACT

Background: Cardiac arrest in children is associated with high morbidity and mortality, primarily due to neurological injury. Biomarkers linked to brain injury, released into circulation from compromised elements of the neurovascular unit, act as significant prognostic indicators in patients suffering from hypoxic-ischemic brain injury (HIBI) subsequent to the restoration of spontaneous circulation (ROSC) after pediatric cardiac arrest. The aim of this systematic review and meta-analysis is to evaluate the prognostic utility of brain injury biomarkers in predicting neurological outcomes and survival in patients following cardiac arrest in the pediatric population.

Methods: Bibliographic databases (PubMed, the Cochrane Library, and Embase) were searched from their inception to November 2024. A random-effect model was used for all analyses.

Results: Our meta-analysis demonstrates significant associations between various biomarkers and survival or neurological outcomes after cardiac arrest. Neuron-specific enolase (NSE) levels were consistently elevated in non-survivors and patients with unfavorable neurological outcomes, with pronounced differences observed on Days 2 and 3 (e.g., Day 3 mean difference: –88.48, 95%CI: –146.77 to –30.19, P = 0.003). Emerging biomarkers, including UCH-L1 and GFAP, showed striking differences, such as elevated UCH-L1 levels on Day 1 (mean difference: –415.41, 95%CI: –474.41 to –356.61, P < 0.001) and GFAP levels exceeding 4000 ng/mL in non-survivors on Day 2 (P < 0.001).

Conclusions: Our findings underscore the significant prognostic value of biomarkers in predicting survival and neurological outcomes following cardiac arrest. Neuron-specific enolase (NSE) consistently demonstrated its reliability across multiple time points, while emerging biomarkers like UCH-L1 and GFAP showed promising potential for early outcome stratification.

Keywords: brain markers; neuron-specific enolase; S100β protein; survival; cardiac arrest; meta-analysis

Introduction

Cardiac arrest in pediatric patients presents a substantial clinical challenge, characterized by a high death rate and a considerable risk of enduring neurological impairment [1]. The primary pathophysiological process resulting in these sequelae is hypoxic-ischemic brain injury (HIBI) [2, 3]. HIBI, resulting from hypoxia and reperfusion, induces intricate biochemical alterations including excitotoxicity, oxidative stress, inflammation, and disruption to the blood-brain barrier. A timely and accurate evaluation of neurological prognosis in this patient cohort is essential for appropriate therapeutic management, facilitating challenging decisions regarding treatment intensity and aiding families in the caregiving process and acceptance of possible clinical outcomes [4, 5].

The pediatric population presents distinct diagnostic and treatment issues owing to its unique developmental characteristics and restricted capacity for accurate clinical assessment. Factors such as anesthesia, intubation, and the absence of definitive reference standards for the maturing nervous system sometimes impede conventional evaluation techniques, including neurological examination and neuroimaging, in this demographic [6]. As a result, there is increasing interest within the scientific community in neurodegenerative biomarkers that can

offer objective and readily interpretable data regarding brain damage and neurological prognosis.

In pediatric cardiac arrest investigations, neuron-specific enolase (NSE), S100β protein, glial fibrillary acidic protein (GFAP), and neurofilament light (NFL) are emerging as some of the most clinically significant neurological biomarkers. NSE, a distinct indicator of neuronal injury, correlates closely with the extent of cerebral damage, whereas S100β, linked to astrocytes, signifies blood-brain barrier impairment and inflammatory activation. GFAP, a marker of astrocytes, signifies structural glial injury, while NFL, found in axons, denotes damage to white matter [7–10].

Research demonstrates differing prognostic significance of various indicators in neurological evaluation. Hoiland et al. illustrated the significant predictive capacity of NFL in assessing neurological prognosis in adult patient's post-cardiac arrest, especially within the 48 hours following the restoration of spontaneous circulation (ROSC) [11]. On the other hand, research by Fink et al. highlighted the usefulness of UCH-L1 and GFAP in pediatric cases, emphasizing their importance in identifying individuals with unfavorable neurological outcomes [8].

Despite encouraging outcomes, limited sample sizes and methodological variability among studies frequently constrain the existing data. The diversity of methods employed, variations in sample intervals, and the absence of standardized cutoff values for biomarkers impede the interpretation of results and their therapeutic utility. Thus, there is a distinct necessity for thorough meta-analyses to consolidate the existing data and develop pragmatic suggestions for practitioners.

This meta-analysis aims to assess the clinical efficacy of neurodegenerative biomarkers in forecasting survival and neurological outcomes in pediatric patients following cardiac arrest.

Methods

We conducted this systematic review in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [12]. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO), with the identification code: CRD42024614708. Given the methods of this investigation, Ethics Committee approval was not required.

Data sources and search strategy

A systematic literature search was performed in PubMed, the Cochrane Library, and Embase databases from inception to November 2024 according to the guidelines of the Cochrane

Collaboration. Keywords used to identify relevant studies were as follows: “ubiquitin carboxyl hydrolase L1” OR “UCH-L1” OR “neuron specific enolase” OR “NSE” OR “S100 beta” OR “S100 calcium” OR “S100 calcium binding protein” OR “neurofilament-light” OR “Nf-L” OR “NFL” OR “glial fibrillary protein” OR “GFAP” OR “Tau” AND “cardiac arrest” OR “out-of-hospital cardiac arrest” OR “OHCA” OR “In-hospital cardiac arrest” OR “heart arrest” OR “cardiopulmonary resuscitation” OR “CPR” OR “sudden cardiac death” AND “pediatric*” OR “paediatric*” OR “child*”. We did not restrict the publication year as long as the record was accessible in the database; however, we limited the search to human studies and articles authored in English. We also examined the reference lists of all included research, prior meta-analyses, and Google Scholar to ensure we did not overlook any eligible studies. We exported the search results to EndNote X9 software (USA) for processing.

Study selection

Studies were included according to the following inclusion criteria:

1) target population: human children between the ages of 1 week and 17 years with cardiac arrest;
2) outcomes: UCH-L1, NSE, NFL, S100B, GFAB, and Tau in the survive vs. decreased groups, or among patients with favorable vs. unfavorable neurological outcome groups;
3) article types: any type of research articles, excluding case reports, reviews, and conference abstracts;
4) language restriction: only articles that were written in English.

We excluded duplicate research or numerous publications of the same study, non-patient studies, and studies with inaccessible data.

Data extraction

For eligible studies, two researchers independently screened the title, abstract, and full text according to predetermined criteria and recorded data in prepared Excel sheets. We resolved any disagreements by discussing with each other or consulting with a third investigator. We extracted the following data from each included study: study characteristics (study name, author, publication year, country) and study group information (numbers, mean age at sampling, mean and standard deviation of biomarkers). For publications lacking sufficient information on predictive accuracy to calculate the 2 × 2 contingency tables, we asked the corresponding authors for help *via* email first and then excluded those studies if we received no response after sending a second email.

Quality assessment

We assessed the methodological quality of included studies using the Newcastle-Ottawa Scale (NOS) [13]. This meant checking whether the following things were true for case-control studies:

1) correct case definition
2) cases that were representative of the whole population
3) choice of control
4) definition of control
5) comparability of case and control groups
6) exposure
7) whether exposure methods were the same for cases and controls
8) non-response rate

A study with a total score of 7 or higher was considered to have a low likelihood of bias. Otherwise, we judged a study with a total score of 6 or less to be biased and removed it from our analysis. Two independent authors (HK and MZ) assessed the quality of the included studies using the remaining nine assessment. Quality rating disagreements were resolved by discussion among all authors.

Data synthesis and meta-analysis

We conducted statistical analysis using STATA (Software for Statistics and Data Science) version 17.0. The effect size of this meta-analysis was expressed as mean differences (MDs) with 95% confidence intervals (CIs). In the case of continuous outcomes, data were reported as median, range, and interquartile range, and we estimated means and standard deviations using the formula described by Hozo et al. [14]. We used Q values and I^2 to test heterogeneity, and $P < 0.10$ was considered to indicate heterogeneity between combined studies. We deemed a P value < 0.10 to be indicative of heterogeneity among the aggregated studies. Furthermore, the interpretation of the I^2 statistic adhered to Cochrane recommendations, categorizing heterogeneity as low (25%), moderate (50%), and high (75%) [15]. If we observed significant heterogeneity, we used a sensitivity analysis that applied the leave-one-out method to identify the study that contributed to the heterogeneity. We assessed publication bias by visually inspecting funnel plots and using Egger's test for meta-analyses with more than 10 included studies. All statistical analyses were two-sided, with a P-value < 0.05 indicating statistical significance.

Results

Overall summary of literature search

The PRISMA chart is presented in Figure 1. Searching multiple databases for titles, abstracts, and keywords returned 371 publications; after deleting duplicates, 216 fulfilled the inclusion and exclusion criteria. After abstract screening, 23 remined for full-text evaluations, and 12 were discarded at this level. Our meta-analysis ultimately included 11 papers [8, 10, 16–24], of which 2 articles represented one study [8, 19]. All 11 papers scored ≥ 7 points on the NOS, indicating high quality (Tab. 1).

The characteristics of eligible studies are summarized in Table 1. The number of subjects in the 10 studies ranged between 21 and 48, with a total sample size of 388 subjects. These studies were from the USA (5 studies), Egypt (2 studies) and one study each from Germany, Korea, and Denmark, with various years of publication spanning 2009–2023.

Findings from meta-analysis

Our meta-analysis reveals significant associations between various biomarkers and survival or neurological outcomes after cardiac arrest (Tab. 2, 3; Fig. 2, 3). Neuron-specific enolase (NSE) levels were consistently higher in patients who died or had unfavorable neurological outcomes. For instance, on Day 3, non-survivors had higher NSE levels (mean: 106.49 ng/mL) than survivors (mean: 23.11 ng/mL), with a mean difference of –88.48 (95%CI: –146.77 to –30.19, P = 0.003). Similarly, higher NSE levels were observed in patients with unfavorable neurological outcomes across multiple time points, particularly on Day 2 (mean difference: –45.66, 95%CI: –59.35 to –31.98, P < 0.001).

For S100B, the results were less consistent. Non-survivors and those with unfavorable outcomes showed higher levels, but the heterogeneity was substantial. On Day 1, S100B levels in survivors and non-survivors were very different (mean difference: –0.46, 95%CI: –0.78 to –0.14, P = 0.005).

Emerging biomarkers, such as UCH-L1, GFAP, and tau, demonstrated potential utility, with striking differences between groups. For instance, UCH-L1 levels on Day 1 were higher in non-survivors (mean: 471.62 ng/mL) compared to survivors (mean: 56.11 ng/mL), with a mean difference of –415.41 ng/mL (95%CI: –474.41 to –356.61, P < 0.001). GFAP also showed pronounced elevation in unfavorable outcomes, with levels exceeding 4000 ng/mL in non-survivors on Day 2, compared to 197.78 ng/mL in survivors (mean difference: –4773.90 ng/mL, 95%CI: –5975.84 to –3571.96, P < 0.001).

Discussion

Our meta-analysis establishes that NSE levels are markedly higher in non-survivors than in survivors, exhibiting a gradual rise from Day 1 to Day 3 following cardiac arrest. This

temporal trend underscores the significant correlation between increased NSE levels, death, and negative neurological consequences. Patients with poor neurological prognoses demonstrated a significant increase in NSE levels, highlighting its function as a marker of neuronal damage. The results validate previous research by Fink et al. [19] and Topjian et al. [24], which identified NSE as a dependable biomarker for neuronal injury and unfavorable outcomes after cardiac arrest. The biomarker's specificity for neuronal tissue is due to its release into the circulation following neuronal cell death, especially under ischemic or hypoxic settings.

Non-survivors and patients with unfavorable neurological outcomes consistently had elevated S100B concentrations, particularly on Days 1 and 3. These findings underscore its vulnerability to early neuronal and astrocytic injury and its function in indicating blood-brain barrier (BBB) compromise. This corresponds with the findings of Shinozaki et al., who emphasized the significance of S100B in evaluating blood-brain barrier integrity and its prognostic implications in ischemic brain injury [25]. Although S100B elevation may partially stem from extra-neural sources, such as peripheral tissue injury, its initial increase is a vital marker for directing post-resuscitation management. We identified significant heterogeneity in our data (up to 97%), suggesting that external variables may influence S100B levels, thus necessitating careful interpretation.

NFL levels demonstrated variety among studies, with certain time points revealing substantial variations, while others failed to attain statistical significance. Axonal injury generates NFL, a cytoskeletal protein, which is associated with the extent of brain damage. Our data indicate that NFL may possess superior prognostic significance for long-term neurological outcomes compared to the acute phase following cardiac arrest. These data align with the findings of Shahim et al., who illustrated the efficacy of NFL in monitoring disease development in chronic neurological illnesses and protracted recovery situations [26].

Individuals with worse neurological outcomes, especially on Days 1 and 2, primarily showed increased UCH-L1 levels. Neuronal injury produces UCH-L1, a neuronal-specific enzyme essential for maintaining protein homeostasis in neurons. These findings align with prior research, including that of Mondello et al., which demonstrated the significance of UCH-L1 in traumatic brain damage [27]. This meta-analysis reveals that, despite the limited number of studies on UCH-L1, its consistent trends highlight its potential as an early prognostic biomarker for neuronal injury in the contexts of ischemia and traumatic brain injury, including cardiac arrest.

The levels of tau protein exhibited a high correlation with poor survival and negative neurological outcomes, aligning with its recognized function as a marker of axonal injury. Tau, a microtubule-associated protein, is released upon axonal injury, and its significance has been thoroughly investigated in neurodegenerative diseases, including Alzheimer's disease. Our results correspond with those of El Husseini et al., who illustrated tau's efficacy in both acute and chronic neurological disorders [28]. Tau's susceptibility to diffuse axonal injury from hypoxic-ischemic encephalopathy renders it a useful biomarker for early prognostication in cardiac arrest. Integrating tau into a multimodal biomarker panel with NSE and S100B may improve prognostic precision.

Significantly increased GFAP levels were noted in patients with poor survival and adverse neurological outcomes, indicating its specificity as a biomarker of astroglia damage. Astrocytic destruction, especially during ischemic brain injury, releases GFAP, an essential intermediate filament protein in astrocytes, into the bloodstream. These results support the conclusions of Berger et al., who emphasized GFAP's elevated sensitivity and specificity in evaluating the severity of brain injury. Nonetheless, discrepancies in test methodologies, patient demographics, and timing of sample acquisition may account for the outlier findings noted in certain investigations.

Limitations

Our meta-analysis has several limitations. A key issue is the heterogeneity across studies, which stems from differences in methodologies, such as study design (prospective vs. retrospective), sample sizes, and patient ages. These discrepancies constrain the comparability of outcomes. A considerable number of the studies we examined had limited sample sizes, diminishing both their statistical power and the capacity to identify meaningful relationships. As a result, the findings from these tiny cohorts may lack generalizability to larger pediatric or adult populations. A further issue is the possibility of research demographic bias, as most studies concentrated on pediatric cardiac arrest cases managed in specialized or tertiary care facilities, which may not accurately represent outcomes in general or resource-limited clinical settings. The prevalence of single-center studies limits the generalizability of findings, as they may not reflect outcomes across varied healthcare systems or populations. Finally, numerous studies concentrated solely on specific biomarkers, such as NSE and S100B, without incorporating these results with additional clinical or imaging data, which may restrict their predictive precision. Mitigating these limitations in subsequent studies would improve the reliability and utility of biomarker data in forecasting outcomes post-cardiac arrest.

Clinical implications

The temporal dynamics of biomarkers in our investigation highlight the necessity for repetitive testing to improve prediction accuracy. Biomarkers, including NSE and S100B, which provide robust early signals, can inform immediate post-resuscitation management, while GFAP and Tau may better reflect long-term outcomes. The significant variation identified in our meta-analysis highlights the necessity for consistent techniques in biomarker sampling and reporting.

Conclusions

This meta-analysis presents fresh information regarding the significance of brain biomarkers, including NFL and tau, as predictive instruments in the clinical assessment of individuals experiencing cardiac arrest. These findings suggest that these biomarkers could enhance conventional neurological assessment techniques, thereby improving care quality for this patient demographic.

Author contributions: Conceptualization: HK and LS.; methodology: HK and LS; software: HK, MZ, and LS; validation: MZ, SG, JK, and LS; formal analysis: HK, KK, MZ, MP, and LS; investigation: HK, MT, KK, MP, PP, and LS; resources: HK, MZ, PP, and LS; data curation: HK, MT, KK, MP, PP, and LS; writing — original draft preparation: HK, PP, MP, KK, and LS; writing — review and editing: HK, MB, SG, MT, SS, NLB, KK, MP, BC, FC, AR, JK, AEM, AL, PP, ZR, WFP, and LS; visualization: HK, MP, and LS; supervision: MZ, BC, WFP, and LS; project administration: HK; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional review board statement: Not applicable.

Informed consent statement: Not applicable.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author (LS).

Acknowledgments: The study was supported by the World Academic Council of Emergency Medicine.

Conflicts of interest: The authors declare no conflict of interest.

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Figure 1. PRISMA flow chart of the included studies

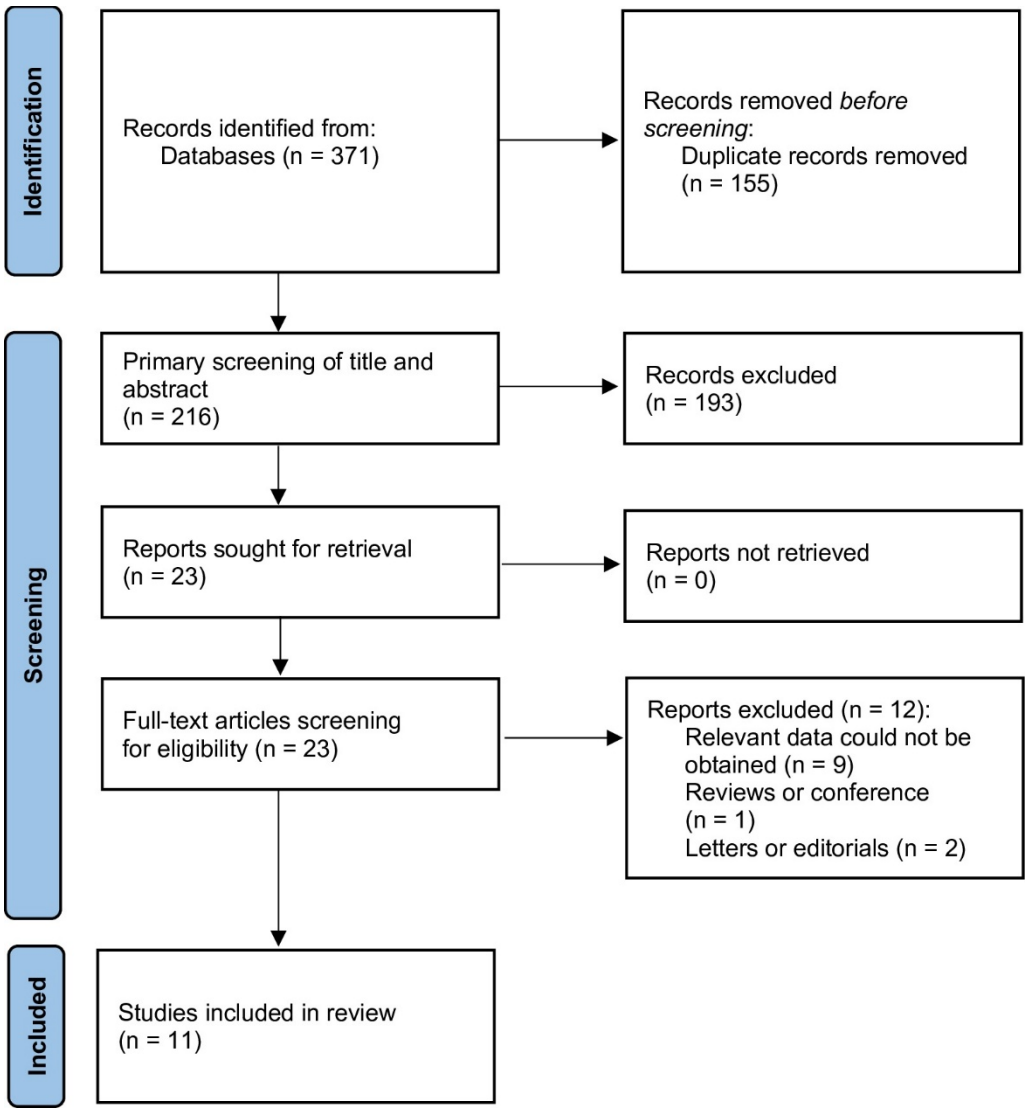
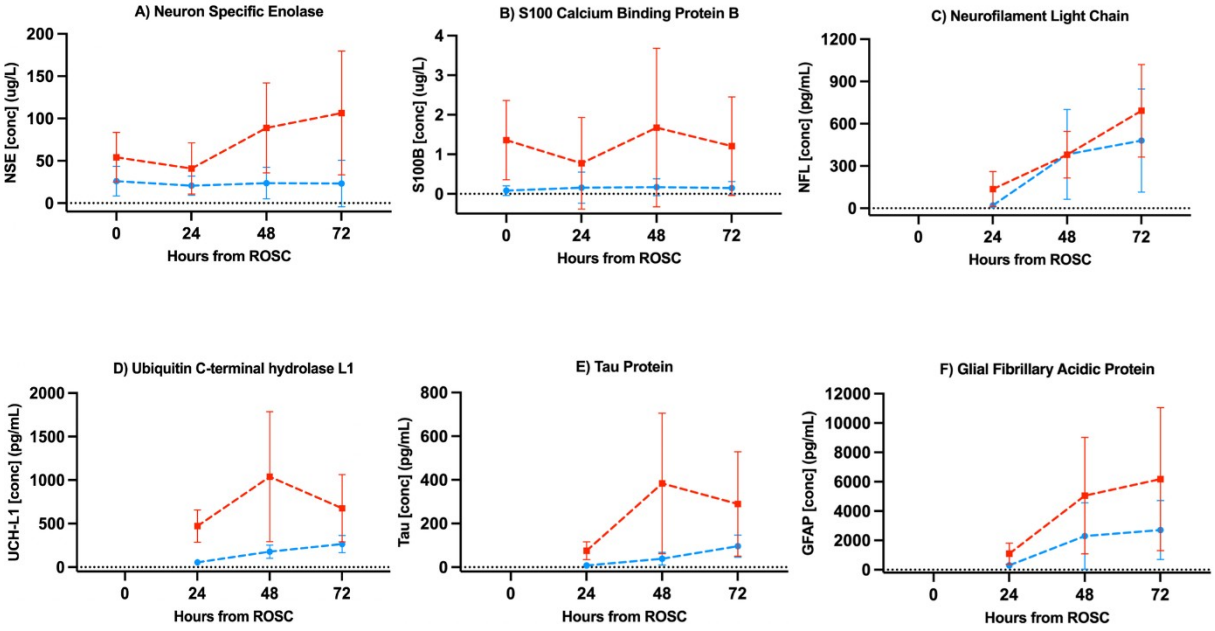
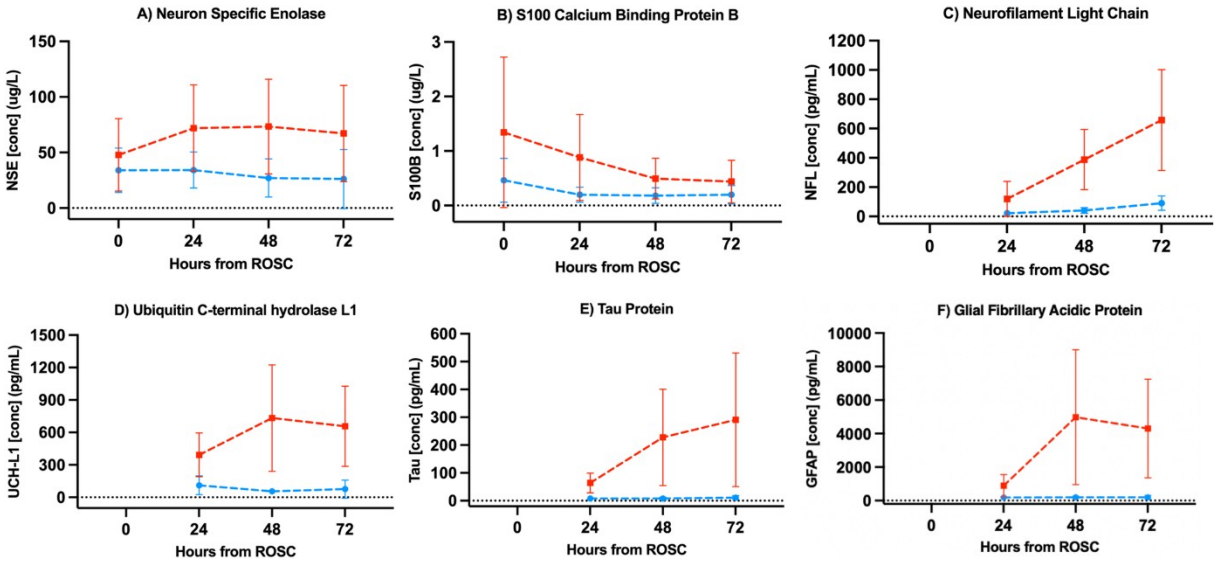


Figure 2. Group differences in brain biomarkers between survivors and patients who died (patients who survived [blue circles] and died [red squares]) outcomes at 0-, 24-, 48-, and 72-hours after return of spontaneous circulation report the mean concentration and spread (SD). Each graph notes the number of patients and studies included in determining the mean and standard deviation for each point



A) Neuron-specific enolase: Y-axis: NSE [conc] (µg/L), X-axis: Hours from ROSC; **B)** S100 Calcium binding protein B: Y-axis: S100B [conc] (µg/L), X-axis: Hours from ROSC; **C)** Neurofilament light chain: Y-axis: NFL [conc] (pg/mL), X-axis: Hours from ROSC; **D)** Ubiquitin C-terminal hydrolase L1: Y-axis: UCH-L1 [conc] (pg/mL), X-axis: Hours from ROSC; **E)** Tau protein: Y-axis: Tau [conc] (pg/mL), X-axis: Hours from ROSC; **F)** Glial fibrillary acidic protein: Y-axis: GFAP [conc] (pg/mL), X-axis: Hours from ROSC

Figure 3. Group differences in brain biomarkers between patients with favorable and unfavorable neurologic outcome (patients with favorable [blue circles] and unfavorable [red squares] outcomes) at 0-, 24-, 48-, and 72-hours after return of spontaneous circulation report the mean concentration and spread (SD). Each graph notes the number of patients and studies included in determining the mean and standard deviation for each point



Biomarkers at different time points after ROSC (return of spontaneous circulation). **A)** Neuron-specific enolase (NSE): Y-axis: NSE [conc] (µg/L), X-axis: Hours from ROSC, Trend: Increase in NSE levels over time, especially in the red dashed-line group; **B)** S100 Calcium binding protein B (S100B): Y-axis: S100B [conc] (µg/L), X-axis: Hours from ROSC, Trend: Initial increase followed by a decrease; **C)** Neurofilament light chain (NFL): Y-axis: NFL [conc] (pg/mL), X-axis: Hours from ROSC, Trend: Significant increase over time, particularly in the red dashed-line group; **D)** Ubiquitin C-terminal hydrolase L1 (UCH-L1): Y-axis: UCH-L1 [conc] (pg/mL), X-axis: Hours from ROSC, Trend: Increase up to 24-48 hours, then stabilization; **E)** Tau protein: Y-axis: Tau [conc] (pg/mL), X-axis: Hours from ROSC, Trend: Significant differences between groups, large variability in values; **F)** Glial fibrillary acidic protein (GFAP): Y-axis: GFAP [conc] (pg/mL), X-axis: Hours from ROSC, Trend: Gradual increase in values over time. *Red dashed line* — possibly indicates a group with poor prognosis. *Blue dashed line* — possibly indicates a group with better prognosis. All graphs represent mean values with confidence intervals

Table 1. Baseline characteristics of included trials

Study	**Country**	**Study design**	**Study group**	**Population**	**Age (y)**	**Sex, female**	**Cardiac etiology**	**Out-of-hospital locat**	**Witnessed event, *n* (%)**	**CPR to ROSC, min**	**NOS score**

								ion			
Abd Elsalam 2018	Egypt	PS	Survived	5	0.245	NS	NS	NS	NS	NS	7
			Died	25	1.252	NS	NS	NS	NS	NS	
Anetakis 2022	USA	Secondary analysis of RCT	Survived	33	1.7 (0.8–9.3)	18 (54.5)	9 (27.3)	21 (63.6)	NS	19 (8–30)	8
			Died	25	3.9 (0.6–14.6)	11 (44.0)	6 (24.0)	20 (80.0)	NS	30 (25–40)	
Bangshøj 2022	Denmark	PS	Survived	20	15 (5–16)	6 (30.0)	3 (15.0)	16 (80.0)	18 (90.0)	21 (10–97)	8
			Died	12	7 (2–15)	4 (33.3)	2 (16.7)	8 (66.7)	7 (58.3)	45 (20–60)	
El-Seify 2023	Egypt	PS	Survived	9	NS	NS	NS	NS	NS	NS	7
			Died	26	NS	NS	NS	NS	NS	NS	
Fink 2014, Fink 2016	USA	PS	Favorable outcome	17	6.53 (6.25)	8 (47.1)	4 (23.5)	11 (64.7)	14 (82.4)	18.0 (16.3)	8
			Unfavorable outcome	26	5.43 (6.42)	13 (50.0)	2 (7.7)	21 (80.8)	6 (23.1)	32.4 (33.2)	
Fink 2022	USA	PS	Favorable outcome	70	1.0 (0–9.0)	28 (40.0)	21 (31.8)	25 (35.7)	65 (92.9)	5.0 (2.0–11.0	8

										)	
			Unfavorable outcome	50	1.0 (0–6.0)	21 (42.0)	12 (29.3)	35 (70.0)	27 (54.0)	29,0 (6.0–40.0)	
Kirschen 2022	USA	RS	Survived	13	8.0 (5.2–13.0)	5 (38.5)	2 (15.4)	6 (46.2)	NS	8.0 (4.8–11.8)	8
			Died	19	8.0 (3.6–13.4)	10 (52.6)	2 (10.5)	16 (84.2)	NS	17.0 (10.0–30.0)	
			Favorable outcome	14	NS	NS	NS	NS	NS	NS	
			Unfavorable outcome	18	NS	NS	NS	NS	NS	NS	
Kramer 2017	Germany	RS	Favorable outcome	48	0.4 (0.09–1.12)	25 (52.1)	46 (95.8)	8 (16.7)	NS	NS	8
			Unfavorable outcome	47	0.62 (0.22–3.6	21 (44.7)	44 (93.6)	5 (10.6)	NS	NS	

					8)						
Lee 2022	Korea	RS	Survived	24	5.5 (0.5–13)	7 (29.2)	8 (33.3)	0 (0.0)	NS	5.0 (2.0–10.0)	8
			Died	32	2.5 (1–8.5)	11 (34.4)	5 (15.6)	0 (0.0)	NS	18.0 (13.7–30.0)	
Topjian 2009	USA	PS	Survived	20	NS	NS	NS	NS	NS	NS	7
			Died	15	NS	NS	NS	NS	NS	NS	
			Favorable outcome	16	NS	NS	NS	NS	NS	NS	
			Unfavorable outcome	19	NS	NS	NS	NS	NS	NS	

NOS — Newcastle-Ottawa scale; NS — not specified; PS — prospective study; RS — retrospective study

Table 2. Pooled analysis of brain biomarkers between survivors and patients who died

Biomarker	**No. of studies**	**Mean ± SD**		**Events**		**Heterogeneity between Trials**	**P-value**
		Survived	**Died**	**MD**	**95%CI**		
Neuron-specific enolase (NSE)							
After ROSC	2	25.94 (17.57)	54.14 (29.42)	–21.26	–27.65 to –14.87	0%	< 0.001
Day 1	5	20.62 (11.29)	40.95 (30.18)	–28.33	–44.53 to –12.12	97%	< 0.001
Day 2	3	23.63	88.96	–70.02	–106.83	92%	<

		(18.86)	(53.09)		to –33.21		0.001
Day 3	3	23.11 (27.54)	106.49 (73.09)	–88.48	–146.77 to –30.19	91%	0.003
S100 Calcium binding protein B (S100B)							
After ROSC	2	0.081 (0.121)	1.358 (1.002)	–1.01	–243 to 0.41	99%	0.16
Day 1	5	0.156 (0.394)	0.773 (1.156)	–0.46	–0.78 to –0.14	94%	0.005
Day 2	3	0.168 (0.213)	1.676 (2.004)	–13.7	–2.42 to –0.31	95%	0.01
Day 3	3	0.146 (0.166)	1.206 (1.247)	–1.08	–1.93 to –0.23	97%	0.01
Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1)							
Day 1	1	56.11 (20.19)	471.62 (186.12)	–415.41	–474.41 to –356.61	NA	< 0.001
Day 2	1	177.22 (76.55)	1039.37 (747.57)	–862.15	–1109.61 to –614.69	NA	< 0.001
Day 3	1	264.66 (98.78)	677.00 (386.01)	–412.34	–569.95 to 254.73	NA	< 0.001
Tau protein (TAU)							
Day 1	1	7.85 (3.38)	75.34 (40.56)	–67.49	–79.87 to –55.11	NA	< 0.001
Day 2	1	38.39 (29.17)	383.54 (321.46)	–345.15	–443.63 to –246.67	NA	< 0.001
Day 3	1	96.63 (50.83)	289.92 (238.92)	–193.10	–284.20 to –102.00	NA	< 0.001
Neurofilament light chain (NFL)							
Day 1	2	20.64 (11.29)	136.54 (124.51)	–139.01	–287.37 to 9.35	93%	0.07
Day 2	1	382.35	379.71	2.64	–257.68	NA	0.98

		(318.48)	(164.96)		to 262.96		
Day 3	1	480.15 (365.75)	692.22 (328.28)	–212.07	–525.43 to 101.29	NA	0.18
Glial fibrillary acidic protein (GFAP)							
Day 1	1	306.77 (82.73)	1097.08 (718.35)	–790.31	–1018.57 to –562.05	NA	< 0.001
Day 2	1	2301.88 (2259.12)	5051 (3071.5)	–2749.12	–4963.88 to –534.36)	NA	< 0.001
Day 3	1	2712.51 (2008.18)	6180.81 (4870.13)	–3468.30	–4798.37 to –175.62	NA	< 0.001

CI — confidence interval; MD — mean difference; NA — not applicable; ROSC — return of spontaneous circulation; SD — standard deviation

Table 3. Pooled analysis of brain biomarkers between patients with favorable and unfavorable neurologic outcome

Biomarker	**No. of studies**	**Mean ± SD**		**Events**		**Heterogeneity between Trials**	**P-value**
		Favorable outcome	**Unfavorable outcome**	**MD**	**95%CI**		
Neuron-specific enolase (NSE)							
After ROSC	2	33.97 (19.97)	47.84 (32.62)	–17.94	–23.32 to –12.55	0%	< 0.001
Day 1	2	34.15 (16.18)	71.94 (39.01)	–37.23	–66.69 to –7.77	92%	0.01
Day 2	3	27.06 (17.21)	73.38 (42.61)	–45.66	–59.35 to –31.98	75%	< 0.001

Day 3	3	26.15 (26.61)	67.13 (43.31)	–40.23	–54.88 to –25.58	65%	< 0.001
S100 Calcium binding protein B (S100B)							
After ROSC	2	0.462 (0.402)	1.343 (1.381)	–0.94	–2.45 to 0.58	98%	0.22
Day 1	3	0.199 (0.138)	0.882 (0.789)	–0.59	–1.16 to –0.03	97%	0.04
Day 2	3	0.182 (0.143)	0.494 (0.374)	–0.32	–0.51 to –0.13	90%	0.001
Day 3	3	0.197 (0.168)	0.438 (0.392)	–0.27	–0.49 to –0.05	93%	0.02
Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1)							
Day 1	2	110.89 (86.85)	392.39 (202.68)	–288.59	-340.65 to -236.53	0%	< 0.001
Day 2	1	55.95 (18.97)	732.65 (491.48)	–676.50	–823.68 to –529.72	NA	< 0.001
Day 3	2	75.64 (83.21)	656.59 (370.74)	–574.88	–684.42 to –465.34	0%	< 0.001
Tau protein (TAU)							
Day 1	1	7.98 (4.24)	64.01 (35.69)	–56.03	–66.18 to –45.88	NA	< 0.001
Day 2	1	7.91 (4.72)	227.82 (172.98)	–219.91	–271.63 to –168.19	NA	< 0.001
Day 3	1	11.19	290.91	–	–	NA	<

		(6.85)	(239.92)	279.72	355.04 to –204.40		0.001
Neurofilament light chain (NFL)							
Day 1	2	21.89 (11.79)	119.75 (118.97)	–104.37	–215.74 to 6.99	92%	0.07
Day 2	1	41.04 (18.88)	387.81 (205.06)	–346.77	–408.24 to –285.30	NA	<0.001
Day 3	1	90.71 (48.6)	657.82 (344.12)	–567.11	–675.87 to –458.35	NA	<0.001
Glial fibrillary acidic protein (GFAP)							
Day 1	2	183.99 (119.99)	890.09 (668.34)	–717.02	–887.34 to –546.69	0%	<0.001
Day 2	1	197.78 (64.36)	4981.68 (4020.96)	–4773.90	–5975.84 to –3571.96	NA	<0.001
Day 3	2	196.76 (117.21)	4299.95 (2943.56)	–3639.34	–5255.93 to –2022.75	80%	<0.001

CI — confidence interval; MD — mean difference; NA — not applicable; ROSC — return of spontaneous circulation; SD — standard deviation