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The role of serum biomarkers as prognostic indicators in pediatric cardiac arrest: A systematic review

Maria Helena Magalhães de Carvalho

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FACULDADE DE **MEDICINA**

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Eu, Maria Helena Magalhães de Carvalho, abaixo assinado, nº mecanográfico 201906970, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração do meu trabalho de Dissertação.

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DESIGNAÇÃO DA ÁREA DO PROJECTO

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The role of serum biomarkers as prognostic indicators in pediatric cardiac arrest: A systematic review

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	X
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Faculdade de Medicina da Universidade do Porto, 19 / 03 / 2025

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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Maria Helena Magalhães de Carvalho, abaixo assinado, nº mecanográfico 201906970, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 19/03/2025

Assinatura conforme cartão de identificação: Maria Helena Magalhães de Carvalho

Dedicatória

Aos meus pais, irmão e família por serem o meu porto seguro em cada etapa desta caminhada.
À Catarina e ao Bernardo, por não me deixarem desistir e acreditarem em mim.
À Semiturma e seus apêndices, por todos os momentos ao longo destes 6 anos.
Aos meus amigos de sempre, que no meio de tantas mudanças, ficaram sempre.
À Doutora Marta pelo apoio incansável ao longo destes meses.

The role of serum biomarkers as prognostic indicators in pediatric cardiac arrest: A systematic review

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Abstract:

Purpose: After Cardiac Arrest (CA), serum biomarkers (SB) are released to the blood in response to the brain damage and, therefore, may be helpful tools to predict neurological outcome. This systematic review aims to assess the role of SB as neurological outcome indicators after pediatric CA.

Methods: A systematic literature search was performed in PubMed, Scopus, WebOfScience and Cochrane Library. All the information retrieved from the selected articles was summarized in a data table.

Results: Eight studies, including a total of 539 patients, were analyzed. Neurological outcomes were assessed using the Pediatric Cerebral Performance Category (PCPC) scale in all studies except one. A total of eleven serum biomarkers were evaluated, with higher concentrations observed in the unfavorable outcome group at various time points. However, only one study defined a specific cut-off value. The biomarkers with the highest predictive accuracy for neurological outcomes appear to be initial levels of IL-17 and CNFT, as well as NSE and S100B.

Conclusion: Following pediatric CA, SB may be helpful indicators of unfavorable neurological outcome, as they seem to appear in higher concentrations in this group. Further research is required to establish specific timepoints and cut-off values and determine the implication of these findings in clinical practice.

Key Words: Pediatrics; Cardiac Arrest; Serum Biomarkers; Neurological Outcome

Introduction

When compared with adult cardiac arrest (CA), pediatric CA is a rare event [6], but when it happens, it is associated with substantial mortality and long-term neurological impairments. Post-CA brain injury is a leading cause of morbidity and mortality, as the brain shows limited tolerance for ischemia [19]. Thus, early determination of neurological prognosis following CA in children has been a critical area of study in pediatric intensive care in the past years.

The assessment of neurological outcome relies on various parameters and different scales are used to evaluate the different domains affected by cerebral lesion. Global neurological status is mostly evaluated by the Pediatric Cerebral Performance Category (PCPC) scale, although some impairments, such as behavioral health and educational challenges may not be detected by these tool [5]. The PCPC scale is a reliable and valid method to describe short-term outcomes in pediatric intensive care and analyzes the overall cognitive impairment of these patients, categorizing them into six groups (normal, mild disability, moderate disability, severe disability, coma or vegetative state and brain death) [4].

Even with the several methodologies available to assess neurological outcome after CA, including neurological examination, somatosensory evoked potentials, electroencephalogram or neuroimaging, a standardized methodology with high sensitivity and early prognostic accuracy for neurological outcome evaluation in children after CA is still lacking [16].

Serum biomarkers (SB) of brain lesion are proteins released from neurons, glia, and astrocytes to the blood in response to the hypoxic-ischemic brain lesion caused by cardiac arrest [15] and, as so, the serum concentration of these biomarkers may reflect the impact of hypoxia and ischemia in the brain tissue cells [19]. These biomarkers could correlate with neurological outcomes, potentially offering an earlier and more accurate method for prognosis, allowing families and doctors to make more informed clinical decisions and optimize treatment strategies.

Across the post-CA adult population, several studies have suggested that SB could serve as valuable prognostic tools. Some studies have already demonstrated that certain biomarkers exhibit high specificity [20] and reliably predict poor neurological outcomes [17], highlighting their emerging potential in guiding post-CA decision-making.

Although some studies suggest that certain SB, such as Neuron-specific Enolase (NSE) may also provide valuable insight for predicting outcomes in pediatric CA [10], available data on pediatric CA remains limited.

Therefore, this systematic review (SR) aims to evaluate the current state of knowledge on the utility of SB as prognostic indicators of neurological outcome in children following CA.

Methods

2.1. Search Strategy and Study Selection

This SR was conducted considering the Preferred Reporting Items for Systematic Reviews e Meta-Analysis (PRISMA) statement [11]. The study protocol was registered on PROSPERO (CRD42024610211).

An extended systematic literature review was performed in PubMed, SCOPUS, WebOfScience and Cochrane Library, on 12 October 2024. Customized search terms and queries were developed for each of the databases and are detailed in Supplementary Table 1.

The first phase of study selection was performed by two authors independently and had in consideration the title and abstracts of all the garnered articles to determine whether they were related or not to this review and exclude duplicates. After the initial screening, full-text articles were retrieved for all the selected studies, and their eligibility was re-assessed taking into consideration both the inclusion and exclusion criteria. If there was a disagreement between the two authors regarding eligibility criteria, a third member was consulted to reach a consensus or, when this was not possible, settle the decision. Additionally, all the bibliographies of the selected articles were screened to ensure that all the relevant publications were analyzed and included. During the selection process, the investigators were not blinded to authors or institutions of the publication.

2.2. Eligibility Criteria

For this SR, the inclusion criteria were delineated as: a) study design, including randomized control trials and retrospective or prospective cohort studies; b) studies performed only in human models; c) the population should include only children (< 18 years old) following CA; d) evaluation of SB after CA must be the focus of the study; e) neurological outcome assessment was performed. As for the exclusion criteria, they were defined as: a) systematic reviews, case reports or commentaries; b) studies performed in animal models; c) studies evaluating the adult population (>18 years); d) if SB after CA were not measured; d) if neurological outcome was not assessed; e) studies that focused their investigation on the diagnosis or the therapeutical intervention of CA. No restrictions were defined regarding publication date or language.

2.3 Data Extraction and Quality Assessment

Each study was individually analyzed by two investigators and data extraction was performed independently for: author information, year of publication, study design, studied population, number of participants, study duration, main outcome, evaluated biomarkers, time of follow-up, methods used to evaluate neurological outcome and statistical methods of each study, as well as relevant results and main conclusions. Risk of bias of the was assessed according to the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (available at *https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools*) and the quality of all selected studies was ranked as “good”, “fair” or “poor”.

Results

The SR identified 182 records and, after eliminating duplicates, 119 titles and abstracts were analyzed. The first phase of selection eliminated 101 articles and only 18 studies met the eligibility criteria for full text review. The investigators had access to all the reports assessed for eligibility and after completing the assessment process, only eight studies were included, involving 539 participants. The study selection process is shown in detail in Figure 1. Quality assessments is summarized in Supplementary Table 2 and classified six of the studies as *Good* and two as *Fair*.

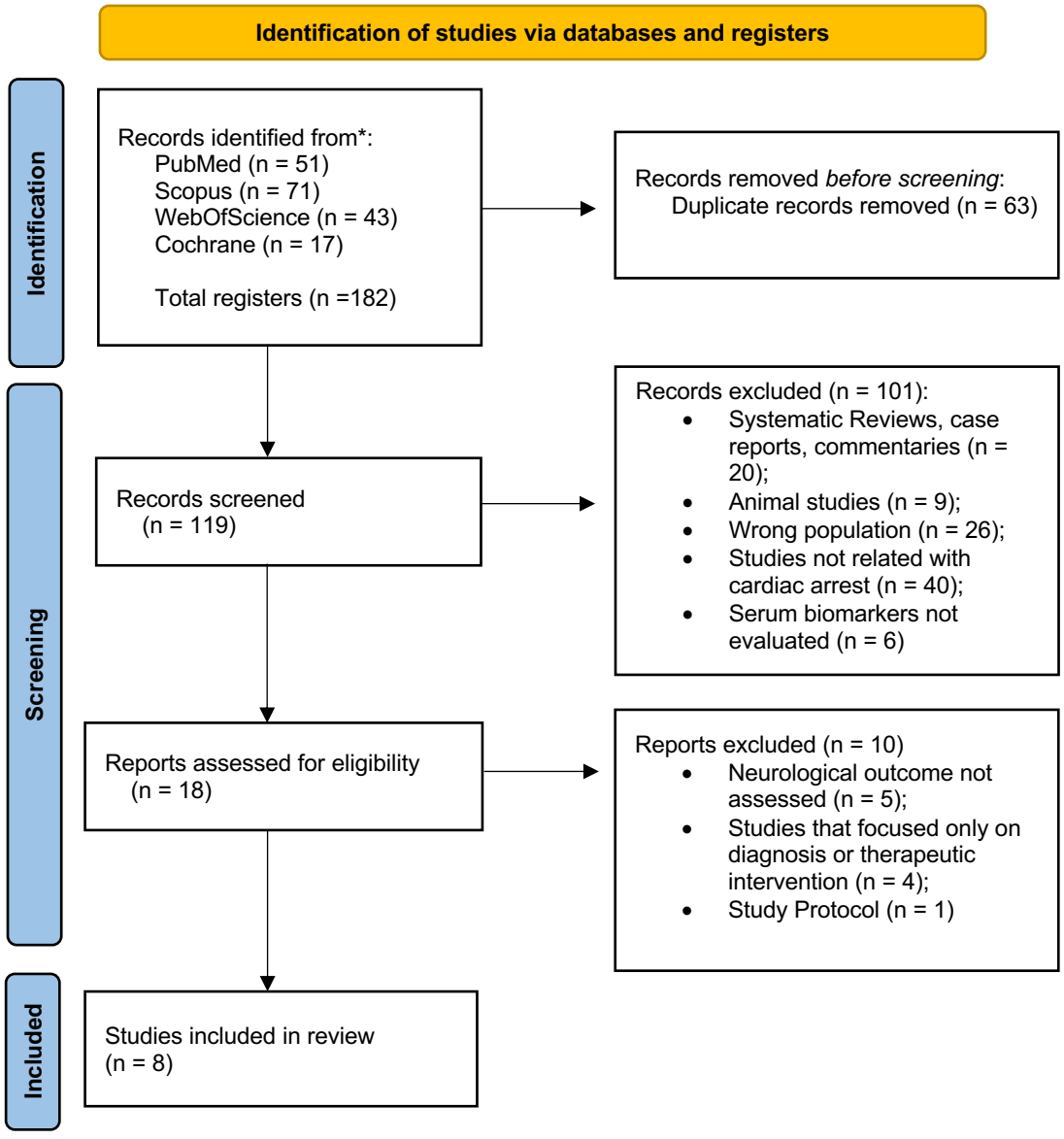

Figure 1. PRISMA 2020 flow diagram for systematic reviews.

The summarized information of the eight included studies is presented in Table 1. All the selected studies were published in English between 2009 and 2024, and seven were carried out in the United States of America (USA) while one was conducted in Germany [9]. Six of the studies

are prospective cohort studies [1-3, 7, 14, 18] and two are retrospective cohort studies [8, 9]. As of patients' characteristics, sample sizes ranged from 39 to 120 and mean age ranged from 0.51 months old to eight years old, although this information was not mentioned in Schwartz et al. [14].

All studies used the Pediatric Cerebral Performance Category (PCPC) scale to characterize neurological outcome, except from Fink et al. (12) that used the Vineland Adaptive Behavior Scales, 3rd edition (VABS-3). However, there was not a consensual definition of favorable or unfavorable outcome among authors. Neurological outcome was assessed at discharge in three of the studies[9, 14, 18], at 6-months post-CA in other three studies [1, 2, 7], one year after CA in one study [3] and the time of evaluation was not detailed in one of the retrospective studies [8].

Various biomarkers were evaluated in the included studies. Ubiquitin Carboxyl-terminal Esterase L1 (UCH-L1)[2, 3, 14], Circulating Neurofilament Light Chain (NfL)[3, 8, 14], Neuron-Specific Enolase (NSE) [1, 9, 18] and S-100b [1, 9, 18] serum concentrations were all evaluated in three studies, whereas both Glial Fibrillary Acidic Protein (GFAP) [2, 3] and Tau [3, 14] were measured in two studies. Ciliary Neurotrophic factor (CNTF) [7], Interleukin-17 (IL-17) [7], Phosphorylated tau 181 (pT181)[14], Plasminogen Activator inhibitor-1 (PAI-1) [18] and Myelin Basic Protein (MBP) [1] were only mentioned in one study each.

Six of the studies used the Area Under the Curve (AUC) statistical method to evaluate whether serum biomarkers were good outcome predictors or not [1-3, 7, 9, 14]. One study calculated the adjusted Odds Ratio (aOR) [3] and other study calculated the Hazard Ratio (HR) [14] of poor neurological outcome. Five studies used Interquartile Range (IQR) to evaluate if there were statistically different values in the poor vs good outcome groups [1, 2, 8, 9, 18]. All biomarkers except from Plasminogen Activator inhibitor-1 (PAI-1) were statistically evaluated according to the AUC.

All the analyzed biomarkers showed superior values in the unfavorable versus favorable group at least once, except from PAI-1, that revealed no significant difference between outcome groups [18].

According to Kernan et al. [7], although IL-17 and CNTF peak levels were both significantly higher in patients with unfavorable outcome at 96h and 168h post-CA respectively, initial IL-17 (AUC 0.85) and initial CNTF (AUC 0.84) were the best predictors of unfavorable outcome.

While Fink et al. [3] indicated that NfL had moderate accuracy (AUC 0.731) on day 1, Schwartz et al. [14] and Kirschen et al [8] didn't corroborate this finding, showing no statistical difference in NfL levels between outcome groups. As for UCH-L1 and GFAP, Fink et al. [2, 3] demonstrated that these two biomarkers were good predictors of unfavorable outcome between days 2 and 3 post-CA. The pT181 biomarker was not significantly associated with increased hazard of unfavorable outcome [14], but higher tau levels were associated with a significantly higher risk of unfavorable outcome [3, 14].

NSE levels were higher in patients with poor neurological outcome, when compared to patients with good outcome in all three studies [1, 9, 18] and Topjian et al. [18] stated that none of the patients with poor neurologic outcome had a NSE level <51µg/L at the statistically significant

times (48h, 72h and 96h). In Kramer et al. [9], the AUC of peak NSE was significantly higher when compared to the conventional parameters (pH, lactate and base excess), demonstrating superior outcome discrimination, the study highlighted that NSE levels 24h after CA were an independent predictor of unfavorable outcome in children, alongside age and duration of CPR.

Topjian et al. [18], found that neither S-100b nor PAI-1 levels differed significantly between outcome groups, but S-100b reached significance at 96 hours post-CA. However, in Kramer et al. [9] and Fink et al. [1], S-100b proved to be a good differentiator of neurological outcome at various time points, showing an AUC of 0.955 to predict the 6 months post-CA outcome. Even though mean, median, and peak serum MBP concentrations were increased in subjects with poor vs good outcome, MBP serum levels only revealed to be a moderate predictor of 6-month neurological outcome (AUC 0.732) [1].

Table 1. Summarized information of the studies included in the systematic review

Authors	Study Design	Number of Participants and Mean Age	Patients' characteristics	Evaluated Biomarkers	Timing of SB's Evaluation	Neurological Outcome Characterization	Statistical Results	Main Conclusions
Kernan et al. [7] 2021	Prospective Observational Single Center Cohort	42 participants with a median age of 2.5 years (0.4-10.2)	Pediatric CA patients admitted to the UPMC between November 2009 and December 2011	CNTF and IL-17	Twice in a 24h period between 0-96h and once approximately at 168h post-CA.	A 6-month follow up PCPC score of 1, 2 or 3 was classified as favorable outcome and a PCPC score of 4, 5 or 6 or an increase >1 between pre-arrest and 6-month post-CA was classified as an unfavorable outcome	Patients with unfavorable outcome had significantly higher initial levels of IL-17 and CNFT. Peak levels were significantly higher in patients with unfavorable versus favorable outcome at 96h post arrest for IL-17 measurement and at 168h for CNFT. The multivariable logistic regression models showed that initial IL-17 and CNFT and peak CNFT each independently associate with outcome ($p<0.05$). Biomarkers with best prediction for unfavorable outcome were initial IL-17 (AUC 0.85 (0.73-0.97), $p<0.001$) and CNFT (AUC 0.84 (0.72-0.96), $p<0.001$). Peak CNFT (AUC 0.78 (0.62-0.95), $p<0.01$) was a moderate to good predictor.	Increased serum CNFT and IL-17 are associated with unfavorable 6-month neurological outcome of children following CA. Further investigations of CNTF and IL-17 pathophysiology in post-CA syndrome are warranted
Fink et al. [3] 2022	Prospective Multicenter Cohort	120 participants with a mean age of 1.0 year (0-8.5)	Patients admitted to a PICU in one of 14 academic referral centers in the US, between May 16, 2017, and August 12,2020, with follow-up through one	GFAP, UCH- L1, NfL and tau	Days 1, 2 and 3 after ROSC	At 1-year post-CA, a favorable outcome was defined as survival with a VABS-3 overall adaptive behavior composite score of 70 points or greater and an unfavorable outcome was defined as a VASB-3 score lower than 70 points or death	Biomarker concentrations were higher in children with unfavorable one year outcome. On day 1, NfL had the best accuracy for 1 year outcome (AUROC 0.731; 95% CI 0.642-0.820). UCH-L1 had the best accuracy for 1 year outcome on day 2 (AUROC 0.860; 95% CI 0.785-0.935) and day 3 (AUROC 0.837; 95% CI 0.747-0.926). Serum concentrations of these biomarkers were associated with unfavorable 1 year outcomes: NfL on post-CA day	Blood-based injury biomarkers, especially NfL at days 2 and 3 after CA, were associated with death or unfavorable adaptive behavior at 1 year after CA with a high degree of accuracy. Evaluation of this accuracy beyond 1 year is needed

			year after enrollment				1 (aOR, 5.91; 95% CI, 1.82-19.19), day 2 (aOR, 1.88; 95% CI, 3.82-36.92), and day 3 (aOR, 10.22; 95% CI, 3.14-33.33); UCH-L1 on day 2 (aOR, 11.27; 95% CI, 3.00-42-36) and day 3 (aOR, 7.56; 95% CI, 2.11-27.09); GFAP on day 2 (aOR 2.31; 95% CI, 1.19-4.48) and day 3 (aOR 2.19; 95% CI, 1.19-4.03); tau on day 1 (aOR 2.44; 95% CI, 1.14-5.25), day 2 (aOR 2.28; 95% CI, 1.31-3.97) and day 3 (aOR 2.04; 95% CI, 1.16-3.57).	
Kirschen et al. [8] 2020	Retrospective Cohort	50 participants with mean age 8.0 years (3.8-13.3)	Patients enrolled in a pediatric ARDS biomarker study at CHOP that received CPR for greater than or equal to 1-minute either prior or during admission to the PICU.	NfL	Within 24h of ARDS onset	Favorable outcome was defined as PCPC score of 1, 2 or unchanged baseline. Unfavorable outcome was characterized as a PCPC score of 3, 4, 5, 6 or a change >=1 from baseline, although timing of evaluation is not detailed	Healthy controls had lower NfL level than patients with CA (5.49 (IQR, 4.96-8.18 vs 30.96 (IQR 11.97-338.64), p<0.001). NfL levels for surviving patients with favorable outcome were not significantly different from patients with unfavorable outcomes and healthy controls.	Further prospective study at serial post-CA time points in a larger pediatric CA population is warranted to assess the utility of NfL as a prognostic biomarker after pediatric CA
Fink et al. [2] 2016	Single Center Prospective Cohort	62 participants with mean age 6.1 years (0-12.8)	Subjects with CA that were enrolled in a RCT at UPMC between November 2009 and September 2011.	UCH-L1 and GFAP	Twice daily from days 1-4 and once on day 7 after ROSC.	At 6 months after CA, a favorable outcome was defined as a PCPC score of 1, 2 or 3. Unfavorable outcome was set as a PCPC score of 4, 5, 6 or death.	Serum UCH-L1 was not different among outcome groups at time point 1 (0.26 (0.15,0.85) vs 0.21 (0.11,0.23) ng/mL-1, p=0.315), but was increased in subjects with unfavorable vs favorable outcome at time point 2 (0.59 (0.27,1.12) vs 0.15 (0.12,0.18) ng/mL-1, p=0.006). Serum GFAP levels at time point 1 did not differ between outcome groups, but subjects with unfavorable outcome had increased serum GFAP versus favorable outcome at time point 2 (2.23 (0.73,16.52) vs 0.00 (0.00,0.42) ng/mL-1, p=0.001). The AUC (95% CI) for serum UCH-L1 to classify 6-month outcome at time point 1 and 2 were 0.782 (0.638-0.925) and 0.822 (0.702-0.942), respectively (p<0.05 for both). The AUC for GFAP was 0.408 (0.238-0.578, p>0.05) for time point 1 and 0.796 (0.642-0.950, p<0.05) for time point 2.	This study suggests that UCH-L1 and GFAP measured at a clinically relevant time point show promising results in prognosticating outcome after pediatric CA. Validation in a larger prospective trial and correlation with other clinical variables associated with outcome after pediatric CA is needed

Schwartz et al. [14] 2024	Prospective Observational Cohort	88 participants of which 46% were neonates (<1month), 27% were infants (1 month to 1 year), 19% were children (1 years to 12 years) and 8% were adolescents (12 years to 18 years);	Pediatric patients supported on ECMO for any indications at two academic ECMO centers between July 2010 and June 2015	NfL, pT181, Tau, UCHL1	First at 24+/-3h from ECMO initiation and then on ECMO days 2 and 3.	A discharge PCPC score >2 with a decline of at least one point from baseline PCPC was considered unfavorable neurological outcome.	Higher level of NfL or pT181 were not significantly associated with increased hazard of unfavorable outcome. Three times higher ECMO day 1 tau levels were significally associated with increased hazard of unfavorable outcome in unadjusted models and after adjusting for age group, sex and pre-ECMO CA status (tau: unadjusted HR, 1.35, 95% CI 1.09-1.66; adjusted HR: 1.42, 95% CI 1.13-1.79). A 3-fold increase in tau levels from ECMO day 1 in serially drawn samples was not associated with unfavorable outcome after adjusting for baseline tau levels, age group, sex and pre-ECMO CA status. The unadjusted model to estimate unfavorable outcome from tau values on ECMO day 1 achieved an AUROC of 0.77 (95% CI: 0.67-0.86)	Brain-specific biomarker tau levels were significally associated with increased hazard of death or unfavorable neurologic outcome in unadjusted and adjusted models. Brain-specific biomarkers, particularly tau, may aid in detection of neurologic injury and neuroprognostication in patients on ECMO with and without preceding CA
Topjian et al. [18] 2009	Prospective Observational Cohort	39 participants with mean age 4 years (0.8-10)	Patients with in or out-of-hospital CA that were admitted to a tertiary care child´s teaching hospital from July 2002 through June 2004	NSE, S-100b and PAI-1	NSE and S-100b were measured at 24, 12, 24, 48, 72 and 96h following CA; PAI-1 was only measured ate 24h following arrest.	Neurological outcome at discharge was categorized as poor if the change in pre- to post arrest PCPC was >=2. Good neurologic outcome was defined as a change in the prearrest PCPC from the post arrest discharge PCPC of <2.	NSE levels were higher in patients with a poor vs good outcome at 48h (45.84 (19.87,97.96) vs 15.38 (7.43, 18.93) µg/L, p<0.001), 72h (25.08 (15.2, 102.13) vs 11.5 (6.354,20.28) µg/L, p<0.001) and 96h (43.55 (23.74,63.9) vs 10.96 (7.29,15.69) µg/L, p<0.001), but there was no significant difference in levels at 4, 12 and 24hrs. None of the patients with poor neurologic outcome had a NSE level of <51µg/L at the statistically significant times. S-100B levels were not significantly associated with poor neurologic outcome at any time point but approached significance at 96hrs (0.51 (0.27,0.66) vs 0.33 (0.25,0.47) µg/L, p=0.01). There was no significant difference between patients with poor and good outcome for total PAI-1 (59.22 (18.4,103) vs 75.9 (36.2,166.5) ng/L; p=0.9) and active PAI-1 (12.62 (6.8, 21.06) vs 38.78 (5.6, 59.04 U/mL; p=0.12).	NSE serum concentration pattern has been shown to correlate with poor neurologic outcome in children following CA. Serum NSE concentrations are associated with neurologic outcome at >=48h and death >=24h. Serum S-100B levels at >=48h are associated with survival. PAI-1 levels at 24hrs were not significally associated with neither neurologic ou survival outcomes.
Kramer et al. [9] 2018	Single Center Retrospective Cohort	95 participants with mean	Children post-CA admitted to a tertiary heart disease	NSE and S-100b	Initially after ROSC or establish	Favorable neurologic outcome was defined as a change	NSE was significantly higher at 24h (88.7 (63.5-135.1)µg/L vs 38.9 (32.7-60.2)µg/L, p<0.001), 48h (89.2 (47.4-146.2)µg/L vs 34.4 (25.0-	Both NSE and S-100b allowed classification of unfavorable neurological outcome,

		age 0.51 years (0-17.1)	center from February 2010 to February 2016		ment of extracor poreal circulato ry support ("initial time point") and at 12, 24, 48 and 72 h after ROSC.	in PCPC score <= 1 at discharge compared to pre-arrest PCPC and unfavorable outcome as a change > 1 or death.	56.8)µg/L, p<0.001) and 72h (89.6 (40.8-150.2)µg/L vs 45.5 (27.8-60.2)µg/L, p=0.005) after CA and S100b was significantly higher initially after ROSC (2.080 (0.670-5.025)µg/L vs 0.545 (0.410-1.453)µg/L, p=0.02) and at 12h (3.610 (0.670-7.860)µg/L vs 0.335 (0.146-0.805)µg/L, p=0.008), 24h (0.610 (0.273-3.558)µg/L vs 0.165 (0.110-0.358)µg/L, p=0.002) and 48h (0.350 (0.235-1.155)µg/L vs 0.140 (0.100-0.235)µg/L, p=0.009) after CA in the unfavorable group compared to favorable group. Both NSE and S-100B showed only marginally superior outcome discrimination in terms of sensitivities, specificities, predictive values and AUC compared to the conventional parameters. Only AUC of peak NSE was significantly higher. NSE 24h after CA was found to be an independent predictor of unfavorable outcome in addition to age and duration of CPR.	despite a variety of confounding factors. 24h NSE value was an independent predictor in multivariable analysis. Further prospective studies are required to investigate their prognostic capacities concerning long-term neurological outcome.
Fink et al. [1] 2014	Prospective Observational Cohort	43 participants with mean age 5.87 years (0.33-11.52)	Subjects after CA admitted at CHOP between November 2009 and September 2001	NSE, S-100b and MBP	Twice daily on days 1-4 and once on day 7 after ROSC	At 6 months post-CA, good neurological outcomes were defined as a PCPC score of 1-3 and poor outcome as a PCPC score of 4-6.	NSE peaked earlier in subjects with good vs poor outcome (30 vs 47.3h, p=0.043). Subjects with good outcome had values within the normal range for all 3 biomarkers. Serum NSE and S100b concentrations were increased in the poor outcome vs good outcome group and in subjects who died vs. survived at 48h, and 72h post-ROSC, all p<0.05. Mean, median and peak serum MBP concentrations were increased in subjects with poor vs good outcome. MBP significantly predicted good vs poor outcome and mortality at 72h. The AUC (95% CI) for serum S100b to predict 6-month outcome was 0.955 (0.922-0.987), the NSE AUC was 0.859 (0.796-0.922) and the MBP AUC was 0.732 (0.647-0.817), all p<0-05.	Serum biomarkers S100b, NSE and MBP have potential to aid in guiding treatment decisions and outcome prediction of children surviving pediatric CA. Modeling and validation of serum and clinical biomarkers may strengthen early prognostication and assist with risk stratification in future clinical studies.

UPMC – University of Pittsburgh Medical Center; PICU – Pediatric Intensive Care Unit; US – United States; ROSC – Return of Spontaneous Circulation; ARDS – Acute Respiratory Distress Syndrome; CHOP – Children's Hospital of Philadelphia; CPR – Cardiopulmonary Resuscitation; RCT – Randomized Control Trial; ECMO – Extra Corporal Membrane Oxygenation;

Discussion

This SR describes the evaluation of SB in children after CA and their correlation with neurological outcome. We found that several biomarkers, such as IL-17, CNTF, NfL, NSE, S-100b and MBP seem to appear in higher serum concentrations in children with poor neurological outcome when compared to those with good neurological outcome. Therefore, it is likely that these biomarkers may be helpful tools, along with the traditional methods, to predict neurological prognosis after pediatric CA. In this SR, Topjian et al. [18] was the only study that defined a SB cut-off value for differentiating between outcome groups, proposing a cut-off serum concentration of 51 µg/L for NSE levels, which implies the need of further studies to determine specific cut-off values for all these biomarkers. Taking all these results in consideration, the biomarkers that seem to have the most accurate discrimination ability between neurological outcome groups are initial levels of Il-17 and CNFT, and NSE and S100b, although the best measurement timepoints are not well defined.

Some systematic reviews and meta-analysis in the adult population [20] had already shown that serum biomarkers, such as NSE and S-100b demonstrated an excellent prognostic value and high specificity in various time points and different populations in predicting neurological outcome, although a specific cut-off value for serum concentration was not yet determined. Other studies have stated that serum biomarkers should be used in combination with other methodologies, in a multimodal approach, reminding the need of developing a standardization for these approaches [12, 13].

At the time of this study, limited information was available on this topic in the pediatric population. However, a previous SR and meta-analysis [10] found that NSE levels between 24h and 72h post-CA were significantly lower in patients with good neurological outcome than in those with poor neurological outcomes, highlighting its potential as a valuable tool to predict outcomes and supporting our findings. Among the SB evaluated in this review, NSE and S-100b appear to be the most promising SB for identifying poor neurological outcomes after pediatric CA.

This SR has some limitations and strengths. Regarding the strengths of this study, to our knowledge, this is the first SR to evaluate, at the same time, various SB as prognostic factors of neurological outcome after CA in the pediatric population. Also, four databases were screened to ensure that all the relevant articles on this topic were included in the SR. Furthermore, most of the included studies are prospective cohort studies which minimizes the probability of information and selection bias when compared to retrospective cohort studies.

As for the limitations, first, most of the included studies were conducted in the USA, so these results may not be applicable in other populations due to genetical, ambiental or socioeconomic differences, such as more delayed healthcare conditions or less accessible healthcare settings. Second, a small number of patients were included, which may compromise the statistical power of the results and impair the interpretation and generalization of these results to the pediatric population. Third, not all studies relied on PCPC to evaluate neurological outcomes and the timing of this assessment was either not mentioned in some studies or ranged from discharge to 1-year post-CA in the others. In addition, the definition of bad versus good neurological outcome was not homogeneous through all the studies, which shows a lack of consensus on this topic.

These limitations emphasize the necessity of developing further studies in different settings, larger pediatric populations and with more standardized methodologies, to evaluate the prognostic value of serum biomarkers in children following CA.

Conclusion

This systematic review concluded that, following CA, patients with poor neurological outcomes generally exhibit higher SB concentrations compared to those with good neurological outcome. While NSE and S-100b appear to have the highest prognostic accuracy, other biomarkers, such as UCH-L1, GFAP and tau are emerging as potential tools to support neurological outcome assessment. Further research is essential to establish precise cut-off values and optimal measurement timepoints for these biomarkers, aiming to develop a standardized multimodal approach for early neurological prognosis in children after CA.

Declarations

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Competing Interests: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Authors Contribution: Conceptualization, study design, literature review and data analysis were performed by Maria Helena Carvalho and Marta João Silva. Maria João Barbosa contributed to reaching consensus on literature revision and supervision. The first draft of the manuscript was written by Maria Helena Carvalho and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Supplementary Material

Supplementary Table 1. Search terms and queries.

PubMed	((Pediatrics OR children OR adolescents) AND (biomarkers OR "serum biomarkers") AND ("neurological prognosis" OR "neurological outcome" OR "brain injury" OR "neurological assessment") AND ("cardiac arrest" OR "post-cardiac arrest" OR "cardiac arrest survivors"))
SCOPUS	(TITLE-ABS-KEY (pediatrics OR children OR adolescents OR youth OR "young patients") AND TITLE-ABS-KEY (biomarkers OR "serum biomarkers" OR "biological markers" OR "inflammatory markers" OR "diagnostic markers" OR "proteomic markers") AND TITLE-ABS-KEY ("neurological prognosis" OR "neurological outcome" OR "brain injury" OR "neurological assessment" OR "neurological recovery" OR "cognitive outcome" OR "neurodevelopmental outcome" OR "functional outcome" OR "long-term prognosis") AND TITLE-ABS-KEY ("cardiac arrest" OR "post-cardiac arrest" OR "cardiac arrest survivors" OR "circulatory arrest" OR "heart arrest" OR "sudden cardiac death"))
WebOfScience	(TS=(pediatrics OR children OR adolescents OR youth OR "young patients") AND TS=(biomarkers OR "serum biomarkers" OR "biological markers" OR "inflammatory markers" OR "diagnostic markers" OR "genetic markers" OR "proteomic markers") AND TS=("neurological prognosis" OR "neurological outcome" OR "brain injury" OR "neurological assessment" OR "neurological recovery" OR "cognitive outcome" OR "neurodevelopmental outcome" OR "functional recovery" OR "neurocognitive outcome" OR "long-term prognosis" OR "functional outcome") AND TS=("cardiac arrest" OR "post-cardiac arrest" OR "cardiac arrest survivors" OR "circulatory arrest" OR "heart arrest" OR "sudden cardiac death"))
Cochrane Library	(pediatrics OR children OR adolescents OR youth OR "young patients") AND (biomarkers OR "serum biomarkers" OR "biological markers" OR "inflammatory markers" OR "diagnostic markers" OR "proteomic markers") AND ("neurological prognosis" OR "neurological outcome" OR "brain injury" OR "neurological assessment" OR "neurological recovery" OR "cognitive outcome" OR "neurodevelopmental outcome" OR "functional outcome" OR "long-term prognosis") AND ("cardiac arrest" OR "post-cardiac arrest" OR "cardiac arrest survivors" OR "circulatory arrest" OR "heart arrest" OR "sudden cardiac death")

Supplementary Table 2. Answers of the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

	Kernan et al. (2021)	**Fink et al. (2022)**	**Kirschen et al. (2020)**	**Fink et al. (2016)**	**Schwartz et al. (2024)**	**Topjian et al. (2009)**	**Kramer et al. (2018)**	**Fink et al. (2014)**
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y	Y
3. Was the participation rate of eligible persons ate least 50%?	Y	N	Y	NR	Y	Y	N	NR
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y	Y	Y	Y	Y	Y
5. Was a sample size justification, power description, or variance and effect estimates provided?	NR	NR	NR	NR	NR	NR	NR	NR
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	Y	Y	Y	Y	Y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	Y	Y	Y	Y	Y	N	Y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA	NA	NA	NA	NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y
10. Was the exposure(s) assessed more than once over time?	Y	Y	Y	Y	Y	Y	Y	Y

11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	NR	Y	Y	Y	Y	Y
12. Were the outcome assessors blinded to the exposure status of participants?	Y	NR	NR	N	NR	N	Y	Y
13. Was loss to follow-up after baseline 20% or less?	Y	N	Y	NR	Y	Y	NR	N
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Y	Y	N	Y	Y	Y	N	Y
Quality Rating	Good	Fair	Good	Good	Good	Good	Fair	Good

Y – Yes; N – No; NR – Not Reported; NA – Not Applicable.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1: "*The role of serum biomarkers as prognostic indicators in pediatric cardiac arrest: A systematic review*"
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	*Purpose: "After Cardiac Arrest (CA), serum biomarkers (SB) are released to the blood in response to the brain damage and, therefore, may be helpful tools to predict neurological outcome. This systematic review aims to assess the role of SB as neurological outcome indicators after pediatric CA. Methods: A systematic literature search was performed in PubMed, Scopus, WebOfScience and Cochrane Library. All the information retrieved from the selected articles was summarized in a data table. Results: Eight studies, including a total of 539 patients, were analyzed. Neurological outcomes were assessed using the Pediatric Cerebral Performance Category (PCPC) scale in all studies except one. A total of eleven serum biomarkers were evaluated, with higher concentrations observed in the unfavorable outcome group at various time points. However, only one study defined a specific cut-off value. The biomarkers with the highest predictive accuracy for neurological outcomes appear to be initial levels of IL-17 and CNFT, as well as NSE and S100B. Conclusion: Following pediatric CA, SB may be helpful indicators of unfavorable neurological outcome, as they seem to appear in higher concentrations in this group. Further research is required to establish specific timepoints and cut-off values and determine the implication of these findings in clinical practice."*
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3 (paragraph 3): "*Even with the several methodologies available to assess neurological outcome after CA, including neurological examination, somatosensory evoked potentials, electroencephalogram or neuroimaging, a standardized methodology with high sensitivity and early prognostic accuracy for neurological outcome evaluation in children after CA is still lacking."* Page 3 (paragraph 4): *"These biomarkers could correlate with neurological outcomes, potentially offering an earlier and more accurate method for prognosis, allowing families and doctors to make more informed clinical decisions and optimize treatment strategies."* Page 3 (paragraph 6): "*Even though some studies have shown that some of these SB, such as Neuron-specific Enolase (NSE) may also provide valuable insight to*

Section and Topic	Item #	Checklist item	Location where item is reported
			predict outcomes in pediatric CA, the current information about CA within the pediatric population is still limited."
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3 (paragraph 7): *"Therefore, this systematic review (SR) aims to evaluate the current state of knowledge on the utility of SB as prognostic indicators of neurological outcome in children following CA."*
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4 (paragraph 4): *"For this SR, the inclusion criteria were delineated as: a) study design, including randomized control trials and retrospective or prospective cohort studies; b) studies performed only in human models; c) the population should include only children (< 18 years old) following CA; d) evaluation of serum biomarkers after CA must be the focus of the study; e) neurological outcome assessment was performed. As for the exclusion criteria, they were defined as: a) systematic reviews, case reports or commentaries; b) studies performed in animal models; c) studies evaluating the adult population (>18 years); d) if serum biomarkers after CA were not measured; d) if neurological outcome was not assessed; e) studies that focused their investigation on the diagnosis or the therapeutical intervention of CA. No restrictions were defined regarding publication date or language."*
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4 (paragraph 2): *"An extended systematic literature review was performed in PubMed, SCOPUS, WebOfScience and Cochrane Library, on 12 October 2024. Customized search terms and queries were developed for each of the databases and are detailed in Supplementary Table 1."*
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 15: *"Supplementary Table1. Search terms and queries."*
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4 (paragraph 3): *"The first phase of study selection was performed by two authors independently and had in consideration the title and abstracts of all the garnered articles to determine whether they were related or not to this review and exclude duplicates. After the initial screening, full-text articles were retrieved for all the selected studies, and their eligibility was re-assessed taking into consideration both the inclusion and exclusion criteria. If there was a disagreement between the two authors regarding eligibility criteria, a third member was consulted to reach a consensus or, when this was not possible, settle the decision. Additionally, all the bibliographies of the selected articles were screened to ensure that all the relevant*

Section and Topic	Item #	Checklist item	Location where item is reported
			publications were analyzed and included. During the selection process, the investigators were not blinded to authors or institutions of the publication."
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4 (paragraph 5): *"Each study was individually analyzed by two investigators and data extraction was performed independently"*
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4 (paragraph 5): "*Each study was individually analyzed by two investigators and data extraction was performed independently for : author information, year of publication, study design, studied population, number of participants, study duration, main outcome, evaluated biomarkers, time of follow-up, methods used to evaluate neurological outcome and statistical methods of each study, as well as relevant results and main conclusion"*
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 4 (paragraph 5): "*Each study was individually analyzed by two investigators and data extraction of was performed independently for : author information, year of publication, study design, studied population, number of participants, study duration, main outcome, evaluated biomarkers, time of follow-up, methods used to evaluate neurological outcome and statistical methods of each study, as well as relevant results and main conclusion"*
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4 (paragraph 5)*: "Risk of bias of the was assessed according to the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (available at* https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools*) and the quality of all selected studies was ranked as "good", "fair" or "poor".*
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and	Page 4 (paragraph 5)*: "Each study was individually analyzed by two investigators"*

Section and Topic	Item #	Checklist item	Location where item is reported
		comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5 (paragraph 2): *"The summarized information of the eight included studies is presented in Table 1".*
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 5 (paragraph 2): *"The summarized information of the eight included studies is presented in Table 1".* Meta-analysis was not performed.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 4 (paragraph 5)*: "Each study was individually analyzed by the investigators and a table was developed with all the relevant data."*
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable.
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable.
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 5 (paragraph 1): *"The SR identified 182 records and, after eliminating duplicates, 119 titles and abstracts were analyzed. The first phase of selection eliminated 101 articles and only 18 studies met the eligibility criteria for full text review. The investigators had access to all the reports assessed for eligibility and after completing the assessment process, only eight studies were included, involving*

Section and Topic	Item #	Checklist item	Location where item is reported
			539 participants." Page 5: *"Figure 1. PRISMA 2020 flow diagram for systematic reviews."*
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 5 (paragraph 1): *"The investigators had access to all the reports assessed for eligibility and after completing the assessment process"*
Study characteristics	17	Cite each included study and present its characteristics.	Pages 7,8,9 and 10: "*Table 1. Summarized information of the studies included in the systematic review"*
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 5 (paragraph 1): *"Quality assessments is summarized in Supplementary Table 2 and classified six of the studies as Good and two as Fair."*
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 7,8,9 and 10: "*Table 1. Summarized information of the studies included in the systematic review"*
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 16: "*Supplementary Table 2. Answers of the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies"*
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable. Meta-analysis was not performed
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 15: "*Supplementary Table 2. Answers of the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies"*

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 16: "*Supplementary Table 2. Answers of the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies*"
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11 (paragraph 1): *"We found that several biomarkers, such as IL-17, CNTF, NfL, NSE, S-100b and MBP seem to appear in higher serum concentrations in children with poor neurological outcome when compared to those with good neurological outcome. Therefore, it is likely that these biomarkers may be helpful tools, along with the traditional methods, to predict neurological prognosis after pediatric CA. In this SR, Topjian et al. was the only study that defined a SB cut-off value for differentiating between outcome groups, proposing a cut-off serum concentration of 51 µg/L for NSE levels, which implies the need of further studies to determine specific cut-off values for all these biomarkers. Taking all these results in consideration, the biomarkers that seem to have the most accurate discrimination ability between neurological outcome groups are initial levels of Il-17 and CNFT, and NSE and S100b, although the best measurement timepoints are not well defined."* Page 12 (paragraph 2): *"This SR concluded that, following CA, patients with poor neurological outcome, generally, show higher SB concentrations when compared to those with good neurological outcome. Although NSE and S-100b seem to have the best prognostic accuracy, other biomarkers such as UCH-L1, GFAP and tau are also arising as potential support tools for evaluating neurological outcomes."*
	23b	Discuss any limitations of the evidence included in the review.	Page 11 (paragraph 5): *"As for the limitations, first, most of the included studies were conducted in the USA, so these results may not be applicable in other populations due to genetical, ambiental or socioeconomic differences, such as more delayed healthcare conditions or less accessible healthcare settings. Second, a small number of patients were included, which may compromise the statistical power of the results and impair the interpretation and generalization of these results to the pediatric population. Third, not all studies relied on PCPC to evaluate neurological outcomes and the timing of this assessment was either not mentioned in some studies or ranged from discharge to 1-year post-CA in the others. In addition, the definition of bad versus good neurological outcome was not homogeneous through all the studies, which shows a lack of consensus on this topic."*
	23c	Discuss any limitations of the review processes used.	Nothing to declare.
	23d	Discuss implications of the results for	Page 12 (paragraph 2): *"Further research is imperative to establish cut-off values and*

Section and Topic	Item #	Checklist item	Location where item is reported
		practice, policy, and future research.	*specific measurement timepoints for these SB, with the aim of developing a standardized multimodal methodology that enables an early determination of neurological prognosis in children after CA."*
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4 (paragraph 1): "*The study protocol was registered on PROSPERO (CRD42024610211)".*
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4 (paragraph 1): "*The study protocol was registered on PROSPERO (CRD42024610211)".*
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	*Page 12 (paragraph 5): "Funding: The authors did not receive support from any organization for the submitted work."*
Competing interests	26	Declare any competing interests of review authors.	Page 12 (paragraph 6): *"Competing Interests: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript."*
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applicable.

Child´s Nervous System
Submission Guidelines

Instructions for Authors

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Review papers may be narrative or systematic and are subject to the peer review process. They should offer exhaustive information on a given subject. The Editor will invite experts in the various fields of the neurosciences to publish Invited papers, although unsolicited reviews may also be considered. The Abstract must not be structured, and the text may be arranged freely. The contribution should not be signed by more than 7 authors, while the text should not exceed 4000 words. Up to 15 figures or tables and 70 references are allowed. Exceptions at the discretion of the Editor in Chief.

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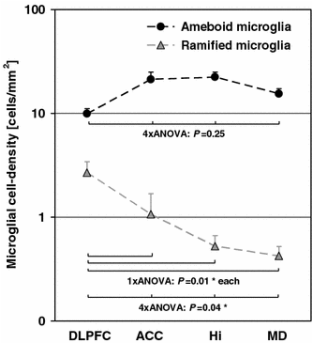

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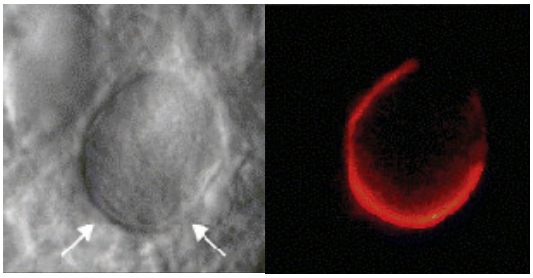

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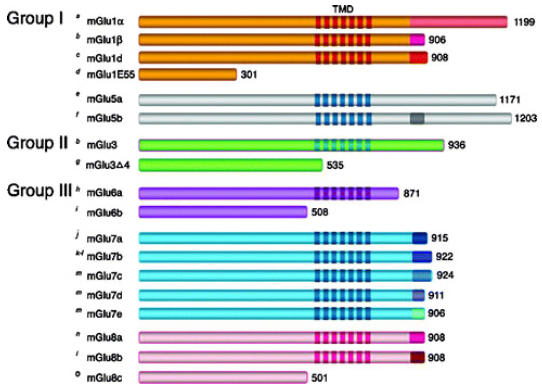

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