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Original Article

Multimodal Neuroprognostication of Poor Neurological Outcomes after Cardiac Arrest: A Systematic Review

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ABSTRACT: ***Background:*** Brain injury related to hypoxic-ischemic insults post-cardiac arrest is a highly morbid and often fatal condition for which neuroprognostication remains challenging. There has been a significant increase in studies assessing the accuracy of multimodal approaches in predicting poor neurological outcomes post-cardiac arrest, and contemporary guidelines recommend this approach. We conducted a systematic review to assess multimodal versus unimodal approaches in neuroprognostication for predicting a poor neurological outcome for adult post-cardiac arrest patients at hospital discharge or beyond. ***Methods:*** PRISMA methodological standards were followed. MEDLINE, EMBASE and CINAHL were searched from inception until January 18, 2024, with no restrictions. Abstract and full-text review was completed in duplicate. Original studies assessing the prognostic accuracy (specificity and false positive rate [FPR]) of multimodal compared with unimodal approaches were included. The risk of bias was assessed using the QUIPS tool. Data were extracted in duplicate. ***Results:*** Of 791 abstracts, 12 studies were included. The FPR in predicting poor neurological outcomes ranged from 0% to 5% using a multimodal approach compared to 0% to 31% with a unimodal test. The risk of bias was moderate to high for most components. ***Conclusions:*** A multimodal approach may improve the FPR in predicting poor neurological outcomes of post-cardiac arrest patients.

RÉSUMÉ : Le pronostic neurologique multimodal d'une évolution défavorable des patients après un arrêt cardiaque : une revue systématique. ***Contexte :*** Les lésions cérébrales liées à l'hypoxie et à l'ischémie après un arrêt cardiaque constituent des dommages associés à une grande morbidité et souvent mortels pour lesquels un pronostic de type neurologique reste difficile à établir. À cet égard, il y a eu une augmentation significative des études évaluant, d'une part, la précision des approches multimodales dans la prédiction de l'évolution neurologique des patients après un arrêt cardiaque et, d'autre part, les lignes directrices contemporaines recommandant cette approche. Nous avons ainsi effectué une revue systématique pour évaluer les approches multimodales par rapport aux approches unimodales dans le cas de pronostics neurologiques permettant de prédire une évolution défavorable chez des patients adultes victimes d'un arrêt cardiaque au moment de leur congé de l'hôpital ou par la suite. ***Méthodes :*** Les normes méthodologiques PRISMA ont été suivies. Des recherches ont été effectuées dans Medline, Embase et CINAHL depuis les débuts de l'étude jusqu'au 18 janvier 2024, et ce, sans aucune restriction. Les résumés et les textes intégraux ont été examinés en double. Des études originales évaluant la précision pronostique (spécificité et taux de faux positifs) des approches multimodales par rapport aux approches unimodales ont été incluses. Le risque de biais a été évalué à l'aide de l'outil QUIPS. De plus, les données ont été extraites en double. ***Résultats :*** Sur 791 résumés, 12 études ont été incluses. Le taux de faux positifs dans la prédiction d'une évolution neurologique défavorable variait de 0 à 5 % en utilisant une approche multimodale contre 0 à 31 % au moyen d'une approche unimodale. Précisons que le risque de biais était modéré à élevé pour la plupart des composants. ***Conclusions :*** Une approche multimodale peut améliorer le taux de faux positifs dans la prédiction d'une évolution neurologique défavorable chez les patients victimes d'un arrêt cardiaque.

Keywords: Neuroprognostication; post-cardiac arrest; poor neurological outcomes; multimodal; adult patients

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Introduction

Cardiac arrest is a major health problem worldwide and is associated with substantial mortality and morbidity. As few as 10% of patients survive to hospital discharge.[1] Most deaths in post-cardiac arrest patients occur following withdrawal of life-sustaining measures (WLSM) because of a predicted poor neurological prognosis.[2] However, advances in management have increased overall survival and rate of discharge with a favorable neurological outcome.[3] As such, consistent, objective and evidence-based neuroprognostication is crucial to avoid inappropriate or premature WLSM. Accurate

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Highlights

- Neuroprognostication after cardiac arrest is challenging.
- A multimodal approach may improve the false positive rate in predicting poor neurological outcomes of post-cardiac arrest patients.
- The ideal number and combination of modalities predicting poor neurological outcomes remains unknown.

neuroprognostication can also circumvent prolonged invasive, potentially harmful and costly therapies that could perpetuate patient and family suffering when there is no realistic chance of a favorable recovery.

The major determinant of prognosis after cardiac arrest remains brain injury related to global ischemia-reperfusion.[3] Assessing the extent of injury and therefore informing prognosis has been a focus of many studies that have investigated the utility of physical examination, neurophysiological testing, serum biomarkers and neuroimaging.[3] However, no single modality has been able to predict a poor outcome for patients with perfect specificity. In addition, all modalities have lacked sensitivity for predicting poor prognosis.[4–7]

To address these concerns, contemporary guidelines[8–11] outline an approach to neuroprognostication that ensures confounders are excluded and sufficient time has passed, while emphasizing a multimodal approach. However, it is still unknown which modalities are best to combine and whether this approach is superior to unimodal assessments. The main objective of this systematic review was to compare the diagnostic accuracy of multimodal approaches versus unimodal tests in the prediction of poor neurological outcomes at hospital discharge and beyond for adult patients who remain comatose post-cardiac arrest.

Methods

This systematic review was conducted according to established methodological standards and reported in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] The protocol was registered in PROSPERO (CRD42022331283) on October 31, 2022.

Literature search

In consultation with a medical librarian, a search strategy was developed (Appendix 1). The search was executed on January 18, 2024, and included three databases (MEDLINE, EMBASE and CINAHL). There were no date or language restrictions. Subject headings (controlled vocabulary) and various full and truncated keywords were combined using Boolean operators and included heart arrest, out-of-hospital cardiac arrest, post-cardiac arrest, prognostication, neuroprognostic, multimodality, multimodal, modalities, pupillary reflex, corneal reflex, electroencephalography (EEG), somatosensory evoked potentials (SSEP), brain CT, brain MRI, neuron-specific enolase (NSE), modified Rankin Scale (mRS), Glasgow Outcome Scale (GOS), treatment outcome and neurological outcomes adult, among others. Reference lists of all papers eligible for full-text review were manually searched to identify additional studies. References were exported and managed using Covidence (Melbourne, Australia).[13]

Eligibility criteria

Patient population

The population of interest was adult (≥18 years old) post-cardiac arrest (in or out-of-hospital) patients. We excluded studies involving only pediatric patients, but those with over 50% adult patients, in addition to pediatric patients aged 16 years or older, were judged acceptable for inclusion. Studies were included regardless of whether patients underwent targeted temperature management (TTM).

Modalities of interest and defined thresholds predictive of a poor prognosis

We utilized contemporary guidelines[8–11] to define modalities of interest and thresholds predictive of a poor prognosis (Appendix 2). Specific criteria for malignant patterns on EEG were defined according to the American Clinical Neurophysiology Society Critical Care EEG Terminology[14] (Table S1). Most studies reported on modalities at multiple time points, which were tracked, even if the timing post-return of spontaneous circulation (ROSC) was not recommended in contemporary guidelines.[8–11]

Multimodal definition

Studies included had to present the prognostic accuracy of a multimodal combination, defined as the use of two or more modalities recommended for unimodal testing in at least one contemporary guideline[8–11] (Table S2). To strengthen our multimodal definition, the tests included had to assess different anatomic or physiologic parameters. Therefore, we excluded studies that only combined CT and MRI. We considered EEG and SSEP as assessing different anatomic and physiologic parameters, as well as myoclonus, pupillary light reflex, corneal reflex and the motor component of the Glasgow Coma Scale (GCS-M). Finally, to be considered multimodal, studies had to combine the modalities, meaning that patients must have been assessed with both (not either) modalities. Thus, studies not meeting this requirement in their multimodal definition[15–17] as well as studies using a Classification and Regression Tree (CART) analysis[18,19] were excluded.

Unimodal definition

We planned to compare multimodal prognostic accuracy to the prognostic accuracy of each individual modality from the same study. Most studies reported on individual modalities at various time points post-arrest. For comparison purposes, we selected the time point for individual modalities with the lowest false positive rate (FPR). If a different threshold for EEG [20,21] or NSE[22] was used for a modality when used alone versus in combination, the threshold with the higher specificity or sensitivity was used in the unimodal analysis. The same approach was used for multimodal tests within each study. GCS-M was not included in the unimodal data analysis as it is no longer approved in recent guidelines to be used in isolation,[8,9,23] unless it was used in the multimodal comparator within the same study.[24–26] However, if GCS-M was part of the entry point of the ERC-ESCIM algorithm, GCS-M was not used in the unimodal analysis as it was not considered part of the multimodal assessment.[21,27,28]

Outcomes

We included studies assessing unfavorable neurological outcomes at hospital discharge or beyond. In studies that reported outcomes at multiple time points, the longest time post-ROSC was chosen for data extraction. The Cerebral Performance Category (CPC) score is the most used in cardiac arrest literature (Table S3).[29] For the purposes of our review, we only included studies that defined poor outcome as CPC 3–5 and favorable outcome as CPC 1–2.[7] If other scores were used, studies had to meet the predefined classification of poor outcomes to be included: mRS 4–6, GOS 1–3 and Glasgow

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Outcome Scale Extended 1–4.[7] We excluded studies that did not use these dichotomizations, unless we were able to obtain the necessary raw data from the authors to reclassify patient outcomes.

Our primary outcome was the FPR with confidence intervals of individual and combinations of tests, in addition to specificity, sensitivity and positive/negative predictive values. For inclusion, studies had to at least report the FPRs or provide sufficient data to allow for these to be calculated. Prior to study exclusion for insufficient data, authors were contacted.

Study selection process

All titles and abstracts were independently screened in duplicate by four reviewers (AB, RH, CB and JK) to identify potentially relevant studies. Abstracts identified by a single reviewer as meeting inclusion criteria were moved to full-text review. Full-text articles were subsequently reviewed in duplicate by three reviewers (AB, RH and CB). Disagreements for eligibility were resolved by the involvement of a third reviewer (JK or AK). In addition to the above outlined inclusion and exclusion criteria, studies were also excluded if they were not original research or when the reference found was a conference abstract only with no corresponding peer-reviewed publication.

Bias assessment

Two blinded reviewers (AB and CB) independently assessed the quality of included studies using the QUIPS tool for systematic reviews of prognostic studies.[30] Each of the six criteria (study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting) has been rated as low, moderate or high risk.[31,32] Disagreements were resolved by the involvement of a third reviewer (JK).

Data extraction and synthesis

All data from included studies were independently extracted and agreed upon in duplicate by two reviewers (AB and CB) using a standardized Microsoft Excel[33] data form created by the study team. Disagreements were resolved by the involvement of a third reviewer (JK or AK). Appendix 3 provides a list of all extracted data.

A meta-analysis was originally planned to use a primary meta-regression to compare specificity between unimodal and multimodal neuroprognostication analyses. A secondary analysis using a similar approach was attempted for sensitivity. A sensitivity analysis was attempted to exclude GCS-M from the primary and secondary analyses as it is no longer a recommended modality in current neuroprognostication guidelines.[8–11] Heterogeneity was assessed using the I^2 statistic and publication bias using funnel plots, Begg's test[34] and Egger's test.[35]

Results

Search results and study selection

A total of 791 studies were identified, 93 of which were duplicates. A total of 698 abstracts were screened and, 362 were excluded. The remaining 336 studies underwent full-text review, with 324 subsequently excluded for reasons outlined in Figure 1. When two or more studies involved patients from the same population and assessed similar multimodal and unimodal approaches, only the study with the larger number of patients was included. After applying inclusion and exclusion criteria, 12 studies remained.

Study characteristics

The characteristics of the 12 included studies are presented in Table 1. There were 4124 patients in total, of which 72% were male,[20–22,24–28,36–39] and the mean age was 61.4 (SD 4.0) years.[20–22,24,25,27,37–39] Three studies reported median ages with interquartile ranges for patients with good and poor outcomes,[26,28,36] and when this dichotomy was used, the median age was 60 (IQR 58.5–61.3) years for patients with good outcomes and 64 (IQR 62.5–64.5) with poor outcomes. Most patients (95%) suffered an out-of-hospital cardiac arrest. Some studies did not report the cause of arrest or the rhythm during cardiac arrest.[21,36] When this information was provided, most patients had a primary cardiac etiology. Average time to ROSC varied between studies from 15 to 30 min, with only a few studies reporting no flow and low flow times. All but two studies used TTM (temperature goal ranging from 32°C to 36°C) in 100% of the patients;[20,21,24–28,36,38,39] TTM was used in 45%[37] and 60%[22] in those studies. CPC was the outcome score used in 11 of 12 studies, reported at either 3[20,24,27,38,39] or 6 months[21,22,24,25,28,37] post-discharge, whereas GOS at 3 months was used in the remaining study.[26] Some studies did not provide any details about causes of death.[26,36,39] WLSM due to a perceived poor prognosis was the main cause of death reported in all but two of the remaining studies; one study excluded patients with WLSM,[28] whereas another did not permit WLSM in their protocol.[37] Details about when decisions regarding WLSM were made were available for two studies.[20,27] However, when actual numbers were given, between 24% and 52%[21,22,24,25] of all included patients underwent WLSM. Details about the causes of death, and other management data are provided in the supplementary data (Table S4).

Study quality assessment

Risk of bias for study participation was rated as low in nine studies[20,22,24,26,28,36–39] and moderate in the remaining three.[21,25,27] Study attrition bias was low[22,24,25,27,28,37–39] in eight studies and moderate in the remaining four.[20,21,26,36] Prognostic factor measurement bias was low in four,[20,28,37,39] moderate in seven[21,22,24,25,27,36,38] and high[26] in one study. Most studies had a low risk of bias pertaining to outcome measurements,[20–22,25–27,36,37,39] although three studies had a moderate risk of bias.[24,28,38] The highest rating in bias assessment was for study confounders, which was high in eight[20,22,24–26,28,36,38] and moderate in the remaining four studies.[21,27,37,39] All studies had a low risk of bias for statistical analysis and reporting.[20–22,24–28,36–39] Details of the assessment for each study are presented in Table 2.

Finally, there may have been publication bias[40] as outlined with Begg's test[34] and Egger's test.[35] Funnel plots (Figures S1 and S2) were also suggestive of the presence of publication bias for the estimate of a pooled specificity (primary analysis) with a unimodal and multimodal approach, both with and without excluding GCS-M (sensitivity analysis). The results of the Egger's test ($t = 4.55$ $p < 0.001$, bias estimate = 1.55 [SE 0.34]) suggested some publication bias of the unimodal specificity for primary analysis and sensitivity analysis ($t = 4.35$, $p < 0.001$, bias estimate = 1.28 [SE 0.30]). Publication bias was also suspected with the multimodal approach specificity for primary and sensitivity analysis using the Begg's test (respectively,

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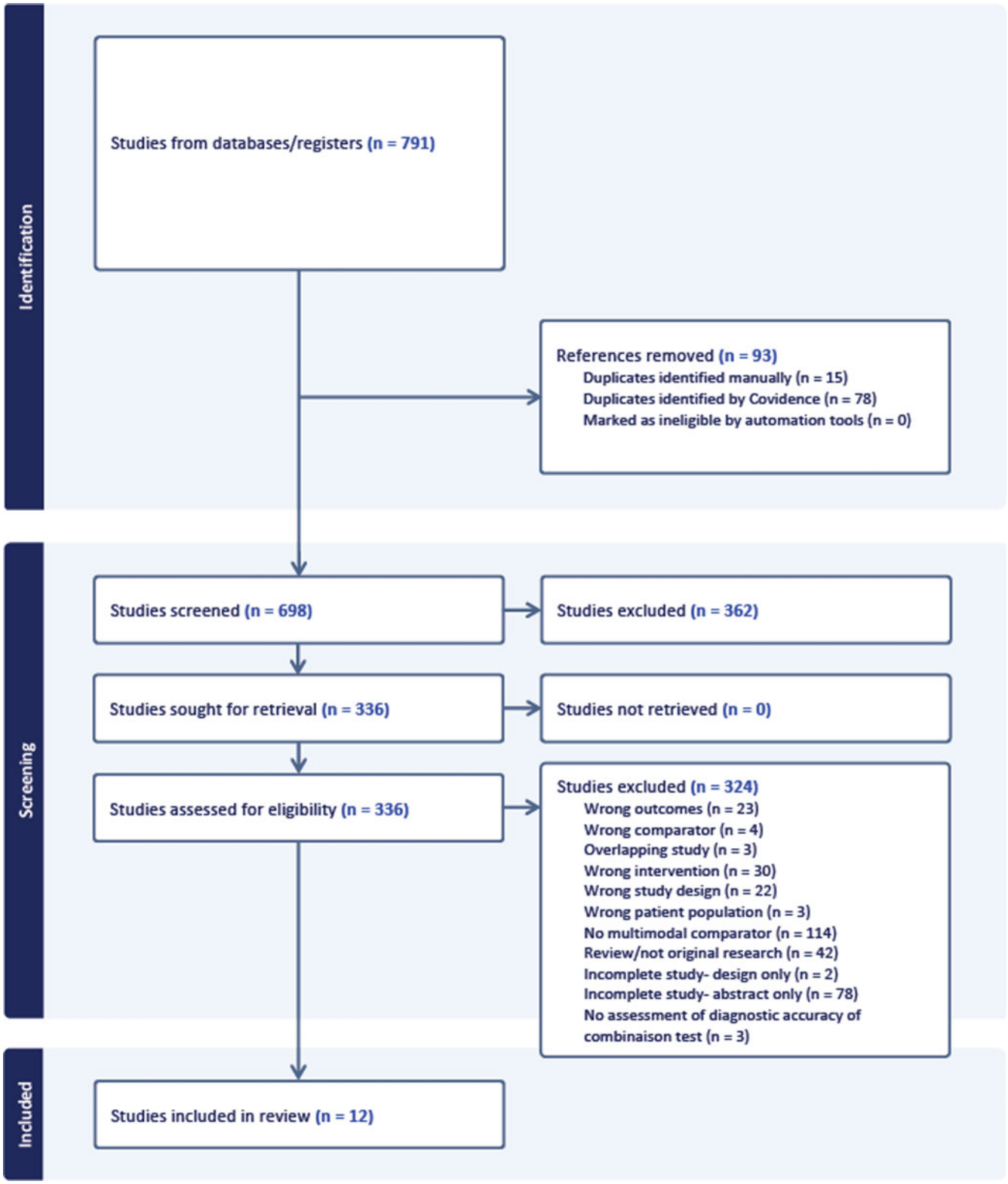

Figure 1. Flowchart of study selection.

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Table 1. Study characteristics

Author, year, country	Number of patients	Age mean [SD] or median (IQR)	Males, n (%)	OHCA, n (%)	Cardiac arrest, n (%)	Shockable (Vfib/VT), n (100%)	Time ROSC (min)	TTM, %	Outcome score and timing
Scarpino, Maenia et al., 2021, Italy [37]	210	64 (18–85)	140 (66.6)	153 (73)	NR	95 (45.2)	21.3 (9–35)	44.8	CPC at 6 months
Ben-Hamouda Nawfel et al., 2022, Switzerland [38]	447	65 (54–74)	312 (69.8)	447 (100)	302 (67.6)	215 (48.1)	NR	100	CPC at 3 months
Youn, Chun Song et al., 2022, Korea [28]	660	GO: 57 (47–66), PO: 61 (50–72)	450 (68.2%)	660 (100%)	346 (52.4%)	161 (24.4%)	GO: 16.0 (10.5–19.0), PO: 29.0 (19.5–40.0)	100	CPC at 6 months
Son, Seung Ha et al., 2020, Korea [39]	58	53.5 (37.6–69.0)	40 (69)	58 (100)	17 (30.4)	19 (33.3)	No flow: 3.5 (0.0–16.0); Low flow: 20.0 (9.0–33.0)	100	CPC at 3 months
Bisschops, Lauren L.A. et al., 2011, Netherlands [26]	103	GO: 62.5 (53.8–70.3) PO: 64 (54.3–76.0)	76 (73.8)	103 (100)	77 (74.8)	72 (69.9)	GO: 15 (10–20), PO 25 (20–45)	100	GOS at 3 months
Kim, Ji Hoon et al., 2020, Korea [24]	715	58 (46–70)	499 (69.8)	715 (100)	430 (60.1)	216 (30.2)	30 (18–42)	100	CPC at 6 months
Zhou, Sonya E. et al., 2019, USA[22]	226	58 [17]	124 (55)	139 (62)	226 (100)	45 (20)	NR	60	CPC at 6 months
Bongiovanni, Filippo et al., 2020, Switzerland [20]	485	64 (54–74)	351 (72.4)	NR	NR	271 (56)	20 (12–30)	100	CPC at 3 months
Moseby-Knappe, Marion et al., 2020, Sweden [21]	585	64 (56–72)	479 (81.9)	585 (100)	NR	473 (80.2)	24 (15–37)	100	CPC at 6 months
Oddo, Mauro et al., 2018, Switzerland [36]	456	GO: 60 (49–69), PO: 65 (54–74)	357 (78.3)	NR	NR	NR	GO: 19 (10–29), PO: 28 (16–41)	100	CPC at 3 months
Pouplet, Caroline et al., 2022, France [27]	49	61.9 (48.7–72.2)	40 (81.6)	45 (91.8)	46 (93.9)	49 (100)	Low flow: 20.0 (12.0–30.0); No flow: 0.0 (0.0–3.0)	100	CPC at 90 days
Roger, Claire et al., 2015, France [25]	130	63.9 [13.7]	90 (70)	130 (100)	67 (51.5)	NR	Low flow <15 min: 45(35%); >15 min: 74 (57%); No flow <5 min: 46 (35%); >5 min: 58 (44%)	100	CPC at 6 months

Note: GO = good outcome; PO = poor outcome; OHCA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation; TTM = targeted temperature management; CPC score = Cerebral Performance Category score; GOS = Glasgow outcome score; NR = not reported.

Table 2. Bias assessment according to QUIPS tool

Author, year	Rating of different bias criteria					
	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Kim, Ji Hoon et al., 2020[24]	Low	Low	Moderate	Moderate	High	Low
Zhou, Sonya E. et al., 2019[22]	Low	Low	Moderate	Low	High	Low
Bongiovanni, Filippo et al., 2020[20]	Low	Moderate	Low	Low	High	Low
Moseby-Knappe, Marion et al., 2020[21]	Moderate	Moderate	Moderate	Low	Moderate	Low
Oddo, Mauro et al., 2018[36]	Low	Moderate	Moderate	Low	High	Low
Pouplet, Caroline et al., 2022[27]	Moderate	Low	Moderate	Low	Moderate	Low
Roger, Claire et al., 2015[25]	Moderate	Low	Moderate	Low	High	Low
Scarpino, Maenia et al., 2021[37]	Low	Low	Low	Low	Moderate	Low
Ben-Hamouda, Nawfel et al., 2022[38]	Low	Low	Moderate	Moderate	High	Low
Youn, Chun Song et al., 2022[28]	Low	Low	Low	Moderate	High	Low
Son, Seung Ha et al., 2020[39]	Low	Low	Low	Low	Moderate	Low
Bisschops, Lauren L.A. et al., 2011[26]	Low	Moderate	High	Low	High	Low

$^{z} = -2.86$, $p = 0.004$, bias estimate = −69.00 [SE 24.15]; $^{z} = -4.01$, $p < 0.001$, bias estimate = −58.00 [SE 14.45]).[40]

Diagnostic accuracy of unimodal tests

Table 3 summarizes the results of the unimodal tests reported in each included study. In studies utilizing clinical examination, GCS-M ≤2 either at 72 h post-rewarming or 72 h post-ROSC had an FPR ranging from 5% to 31%,[24–26] whereas bilaterally absent PLR and/or CR at 72 h or 108 h post-ROSC had an FPR ranging from 0 to 6%[21,22,24,25,27,28,36–38] in predicting poor neurological outcomes. The study by Oddo et al. was the only one using pupillometry and demonstrated that NPi ≤2 at 72 h had an FPR of 0% (95% CI 0.0–3.5) in predicting poor outcomes, while standard PLR was not as specific (94%, FPR 6% [95% CI 2.1–14.3]).[36] Status myoclonus had an FPR ranging from 0% to 11% depending on timing post-ROSC within 48–72 h[21,22,27,37,38] or 7 days post-ROSC.[26] NSE greater than 33 mcg/L within 6–72 h post-ROSC resulted in an FPR between 0% and 5%.[20–22,27,28,38,39] For neuroimaging, CT head within 10–72 h post-ROSC showing either gray-to-white matter ratio <1.07–1.21 or generalized edema with a reduced differentiation between gray and white matter had an FPR between 0% and 9%.[21,22,28,37,39] Brain MRI showing signs of significant anoxic brain injury between 6 h and 2 weeks post-ROSC had an FPR ranging from 0% to 12%.[21,22,28,39] Using either CT head or brain MRI showing diffuse anoxic brain injury at 72 h post-ROSC resulted in an FPR of 0% (95% CI 0.0–60.2) in predicting poor outcomes in one study.[27] Highly malignant patterns on EEG predicted poor outcomes accurately, with an FPR of 0%–3% when EEG was performed within 24–72 h[20–22,27,28,37,38] and as high as 25% when EEG was performed within 2 weeks post-ROSC.[26] Finally, SSEP showing bilaterally absent N20 wave or absence on one side and a pathological N20 potential on the other side at least 24 h post-ROSC demonstrated an FPR of 0–1%.[21,26,28,36–38]

Modalities found in individual studies to have an FPR of 0% while also having a sensitivity of ≥50% were NSE >78.9 mcg/L 48–72 h post ROSC,[22] NSE >60 mcg/L 72 h post ROSC,[27] bilaterally absent PLR 72 h post-ROSC,[25] SSEP with absent N20 wave on one side with pathological N20 wave on the other side at 72 h post-ROSC,[37] bilateral absent CR and PLR 72 h post-ROSC,[28] bilaterally absent N20 on SSEP at 24 h post-ROSC,[28] highly malignant patterns on EEG at 24 h post-ROSC[28] and brain MRI with generalized edema 48–168 h post-ROSC.[28] However, sensitivities and specificities for the same modalities using similar thresholds and timing of assessment were quite variable between studies.

Diagnostic accuracy of multimodal combination of tests

A summary of the multimodal combinations used for each study, with their diagnostic accuracy, is presented in Table 4. All multimodal combinations had an FPR ≤5% for predicting poor outcomes in comatose post-arrest patients. The highest FPRs were seen with the combinations of GSC-M and PLR at 72 h post-ROSC[25] (FPR 4.5% [95% CI 0.1–22.8]), GCS-M combined with CR at 72 h post-rewarming (FPR 2.1% [95% CI 0.6–5.2])[24] and any combination of two modalities including PLR, SSEP, EEG, NSE or myoclonus between 24 h and 72 h post-ROSC (FPR 0.6% [95% CI 0.0–3.6]).[38] Ten studies used combinations resulting in an FPR of 0%.[20–22,24,26–28,36,37,39] Many studies used the 2015 ERC-ESICM algorithm[23] or a slightly modified version excluding GCS-M as a multimodal predictor,[20–22,37] whereas other studies[27,28] used the 2021 ERC-ESICM algorithm.[9] Combinations of clinical examination using GCS-M, CR and/or PLR were used in three studies.[24–26] Oddo et al. found that the combination of NPi with SSEP at 48–72 h led to an FPR of 0% (95% CI 0.0–5.6).[36] NSE >54.8 ng/mL was combined with either brain CT or brain MRI within 6 h post-cardiac arrest and had similar results.[39]

The combinations leading to an FPR of 0% while also having a sensitivity ≥50% were GCS-M ≤2 and bilaterally absent PLR at 72 h post-rewarming,[24] bilaterally absent PLR and CR at 72 h post-rewarming,[24] GCS-M ≤2 with bilaterally absent PLR and CR at 72 h post-rewarming,[24] 2015 ERC-ESCIM without GCS-M with modalities assessed between 24 and 72 h post-ROSC,[20,37] 2021 ERC-ESCIM with modalities assessed 24 h to 7 days post-ROSC,[27,28] NPi ≤2 with bilateral

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Table 3. Diagnostic accuracy of unimodal data utilized in analysis

Author, year	Modality	Timing (h)*	Threshold used to predict poor outcome	Number of patients	FP	FN	TP	TN	Sens % (95% CI)	Spec % (95% CI)	FPR % (95% CI)	PPV % (95% CI)	NPV% (95% CI)
Kim, Ji Hoon et al., 2020[24]	GCS-M	72 post-rewarming	GCS-M ≤2	462	17	31	237	177	88.4 (84.0–92.0)	91.2 (86.3–94.8)	8.8 (5.2–13.7)	93.3 (89.5–96.1)	85.1 (79.5–89.6)
	PLR	72 post-rewarming	Absent bilaterally	463	2	106	162	193	60.4 (54.3–66.3)	99.0 (96.3–99.9)	1.0 (0.1–3.7)	98.8 (95.7–99.0)	64.5 (58.8–70.0)
	CR	72 post-rewarming	Absent bilaterally	398	10	61	177	150	74.4 (68.3–79.8)	93.8 (88.8–97.0)	6.2 (3.0–11.2)	94.7 (90.4–97.4)	71.1 (64.5–77.1)
Zhou, Sonya E. et al., 2019[22]	PLR	72	Absent bilaterally	206	2	124	49	31	28.3 (21.7–35.7)	93.9 (79.8–99.3)	6.1 (0.7–20.2)	96.1 (86.5–99.5)	20.0 (14.0–27.2)
	SM	≤72	Myoclonic status epilepticus (continuous, repetitive myoclonic jerks lasting more than 30 min)	226	1	134	59	32	30.6 (24.2–37.6)	97.0 (84.2–99.9)	3.0 (0.1–15.8)	98.3 (91.1–100.0)	19.3 (13.6–26.1)
	EEG	>24	Burst suppression	197	0	149	24	24	13.9 (9.1–19.9)	100.0 (85.8–100.0)	0.0 (0.0–14.2)	100.0 (85.8–100.0)	13.9 (9.1–19.9)
	NSE	48–72	>78.9 mcg/L	34	0	15	15	4	50.0 (31.3–68.7)	100.0 (39.8–100.0)	0.0 (0.0–60.2)	100.0 (78.2–100.0)	21.1 (6.1–45.6)
	Brain CT	≤24	Reduced GWR	180	0	132	22	26	14.3 (9.2–20.8)	100.0 (86.8–100.0)	0.0 (0.0–13.2)	100.0 (84.6–100.0)	16.5 (11.0–23.2)
	Brain MRI	48–144	Diffuse hypoxic-ischemic injury	96	2	20	59	15	74.7 (63.6–83.8)	88.2 (63.6–98.5)	11.8 (1.5–36.4)	96.7 (88.7–99.6)	42.9 (26.3–60.6)
Bongiovanni Filippo et al., 2020[20]	NSE	24–48	Peak NSE >75 mcg/L	356	1	125	19	211	13.2 (8.1–19.8)	99.5 (97.4–100.0)	0.50 (0.0–2.6)	95.0 (75.1–99.9)	62.8 (57.4–68.0)
	EEG	48	Highly malignant: suppressed background without discharges, suppressed background with continuous periodic discharges, burst suppression background with or without discharges	356	1	118	26	211	18.1 (12.1–25.3)	99.5 (97.4–100.0)	0.50 (0.0–2.6)	96.3 (81.0–99.9)	64.1 (58.7–69.3)
Moseby-Knappe, Marion et al., 2020[21]	PLR/CR	≥108	Both bilaterally absent	301	0	203	51	47	20.1 (15.3–25.5)	100.0 (92.5–100)	0.0 (0.0–7.5)	100.0 (93.0–100.0)	18.8 (14.2–24.2)
	SSEP	84–108	Bilaterally absent N20 potentials on short latency	200	1	88	73	38	45.3 (37.5–53.4)	97.4 (86.5–99.9)	2.6 (0.1–13.5)	98.6 (92.7–100.0)	30.2 (22.3–39.0)
	NSE	48 and/or 72	≥ 48 pg/mL at 48 h and/or ≥ 38 pg/mL at 72 h	646	12	123	186	325	60.2 (54.5–65.7)	96.4 (93.9–98.1)	3.6 (1.9–6.1)	93.9 (89.7–96.8)	72.5 (68.2–76.6)
	EEG	48–72	Highly malignant: suppressed background with or without periodic discharges or burst suppression with or without discharges	305	1	137	84	83	38.0 (31.6–44.8)	98.8 (93.5–100.0)	1.2 (0.0–6.5)	98.8 (93.6–100.0)	37.7 (31.3–44.5)
	SM	≥48	Status myoclonus >30 min	933	1	459	34	439	6.9 (4.8–9.5)	99.8 (98.7–100.0)	0.2 (0.0–1.3)	97.1 (85.1–99.9)	48.9 (45.6–52.2)
	Brain CT	10 (2–81)	Visually evaluated generalized edema seen as a reduced differentiation between gray and white matter	356	2	159	76	119	32.3 (26.4–38.7)	98.3 (94.2–99.8)	1.7 (0.2–5.8)	97.4 (91.0–99.7)	42.8 (36.9–48.9)

(*Continued*)

Table 3. Diagnostic accuracy of unimodal data utilized in analysis (*Continued*)

Author, year	Modality	Timing (h)*	Threshold used to predict poor outcome	Number of patients	FP	FN	TP	TN	Sens % (95% CI)	Spec % (95% CI)	FPR % (95% CI)	PPV % (95% CI)	NPV% (95% CI)
	Brain MRI	214 (147–320)	Presence of generalized edema	35	0	20	3	12	13.0 (2.8–33.6)	100.0 (73.5–100.0)	0.0 (0.0–26.5)	100.0 (29.2–100.0)	37.5 (21.1–56.3)
Oddo, Mauro et al., 2018[36]	Pupillometry (NPi)	72	NPi ≤2	271	0	139	28	104	16.8 (11.4–23.3)	100.0 (96.5–100.0)	0.0 (0.0–3.5)	100.0 (87.7–100.0)	42.8 (36.5–49.3)
	PLR	72	Bilaterally absent	206	5	105	23	73	18.0 (11.7–25.7)	93.6 (85.7–97.9)	6.4 (2.1–14.3)	82.1 (63.1–93.9)	41.0 (33.7–48.6)
	SSEP	48–72	Bilaterally absent N20 wave	188	0	69	64	55	48.1 (39.4–56.9)	100.0 (93.5–100.0)	0.0 (0.0–6.5)	100.0 (94.4–100.0)	44.4 (35.4–53.5)
Pouplet, Caroline et al., 2022[27]	PLR/CR	72	Both bilaterally absent	44	0	18	1	25	5.3 (0.1–26.0)	100.0 (86.3–100.0)	0.0 (0.0– 13.7)	100.0 (2.5–100.0)	58.1 (42.1–73.0)
	EEG	>24	Highly malignant patterns (suppressed background ± periodic discharges or burst suppression)	28	0	10	9	9	47.4 (24.4–71.1)	100.0 (66.4–100.0)	0.0 (0.0–33.6)	100.0 (66.4–100.0)	47.4 (24.4–71.1)
	NSE	72	>60 µg/L	48	0	10	12	26	54.5 (32.2–75.6)	100.0 (86.8–100.0)	0.0 (0.0–13.2)	100.0 (73.5–100.0)	72.2 (54.8–85.8)
	SM	≤48	Continuous and generalized myoclonus persisting ≥30 min	49	1	17	6	25	26.1 (10.2–48.4)	96.2 (80.4–99.9)	3.8 (0.1–19.6)	85.7 (42.1–99.6)	59.5 (43.3–74.4)
	Brain CT/ brain MRI	≤ 72/48–168	Diffuse anoxic injury	12	0	5	3	4	37.5 (8.5–75.5)	100.0 (39.8–100.0)	0.0 (0.0–60.2)	100.0 (29.2–100.0)	44.4 (13.7–78.8)
Roger, Claire et al., 2015[25]	GCS-M	72	<3	71	1	3	47	20	94.0 (83.5–98.7)	95.2 (76.2–99.9)	4.8 (0.1–23.8)	97.9 (88.9–99.9)	87.0 (66.4–97.2)
	PLR	72	Bilaterally absent	61	0	17	18	26	51.4 (34.0–68.6)	100.0 (86.8–100.0)	0.0 (0.0–13.2)	100.0 (81.5–100.0)	60.5 (44.4–75.0)
Scarpino, Maenia et al., 2021[37]	PLR	72	Bilaterally absent	210	3	84	80	43	48.8 (40.9–56.7)	93.5 (82.1–98.6)	6.5 (1.4–17.9)	96.4 (89.8–99.2)	33.9 (25.7–42.8)
	SSEP	72	Absent N20 wave on one side, pathological N20 wave on the other side	210	0	79	85	46	51.8 (43.9–59.7)	100.0 (92.3–100.0)	0.0 (0.0–7.7)	100.0 (95.8–100.0)	36.8 (28.4–45.9)
	EEG	72	Malignant EEG: isoelectric, suppression or burst suppression	210	0	87	78	46	47.3 (39.5–55.2)	100.0 (92.3–100.0)	0.0 (0.0–7.7)	100.0 (95.4–100.0)	34.6 (26.6–43.3)
	Brain CT	≤24	GWR <1.21	210	0	107	57	46	34.8 (27.5–42.6)	100.0 (92.3–100.0)	0.0 (0.0–7.7)	100.0 (93.7–100.0)	30.1 (22.9–38.0)
	SM	≤72	Continuous and generalized myoclonic jerks persisting for at least 30 min	210	0	160	4	46	2.4 (0.7–6.1)	100.0 (92.3–100.0)	0.0 (0.0–7.7)	100.0 (39.8–100.0)	22.3 (16.8–28.6)
Ben-Hamouda, Nawfel et al., 2022[38]	PLR	72	Absent bilaterally	439	6	179	87	167	32.7 (27.1–38.7)	96.5 (92.6–98.7)	3.5 (1.3–7.4)	93.5 (86.5–97.6)	48.3 (42.9–53.7)
	EEG	36–72	Highly malignant (suppressed background with or without repetitive epileptiform discharges and burst suppression with or without discharges)	396	4	168	74	150	30.6 (24.8–36.8)	97.4 (93.5–99.3)	2.6 (0.7–6.5)	94.9 (87.4–98.6)	47.2 (41.6–52.8)
	SM	<72	Present (no specific definition given)	438	2	206	61	169	22.8 (17.9–28.4)	98.8 (95.8–99.9)	1.2 (0.1–4.2)	96.8 (89.0–99.6)	45.1 (40.0–50.3)
	NSE	Within 48	Highest NSE level >60 mcg/L	407	2	142	105	158	42.5 (36.3–48.9)	98.8 (95.6–99.8)	1.2 (0.1–4.4)	98.1 (93.4–99.8)	52.7 (46.8–58.4)

Table 3. Diagnostic accuracy of unimodal data utilized in analysis (*Continued*)

Author, year	Modality	Timing (h)*	Threshold used to predict poor outcome	Number of patients	FP	FN	TP	TN	Sens % (95% CI)	Spec % (95% CI)	FPR % (95% CI)	PPV % (95% CI)	NPV% (95% CI)
	SSEP	>24 (after ending TTM)	Bilaterally absent N20	392	1	148	95	148	39.1 (32.9–45.5)	99.3 (96.3–100.0)	0.7 (0.0–3.7)	99.0 (94.3–100.0)	50.0 (44.2–55.8)
Youn, Chun Song et al., 2022[28]	PLR/CR	≥72	Both bilaterally absent	518	0	166	281	71	62.9 (58.2–67.4)	100.0 (94.9–100.0)	0.0 (0.0–5.1)	100.0 (98.7–100.0)	30.0 (24.2–36.2)
	SSEP	≥24	Bilaterally absent N20	150	0	36	96	18	72.7 (64.3–80.1)	100.0 (81.5–100.0)	0.0 (0.0–18.5)	100.0 (96.2–100.0)	33.3 (21.1–47.5)
	NSE	48 and/or 72	>60 mcg/L	363	3	65	242	53	78.8 (73.8–83.3)	94.6 (85.1–98.9)	5.4 (1.1–14.9)	98.8 (96.5–99.7)	44.9 (35.7–54.3)
	EEG	>24	Highly malignant: suppressed background, suppressed background with continuous periodic discharges and burst suppression background	249	0	84	122	43	59.2 (52.2–66.0)	100.0 (91.8–100.0)	0.0 (0.0–8.2)	100.0 (97.0–100.0)	33.9 (25.7–42.8)
	Brain CT	≤ 72	Poor CT: Generalized edema	602	9	338	165	90	32.8 (28.7–37.1)	90.9 (83.4–95.8)	9.1 (4.2–16.6)	94.8 (90.4–97.6)	21.0 (17.3–25.2)
	Brain MRI	48–168	Poor MRI: Generalized edema	332	0	62	220	50	78.0 (72.7–82.7)	100.0 (92.9–100.0)	0.0 (0.0–7.1)	100.0 (98.3–100.0)	44.6 (35.2–54.3)
Son, Seung Ha et al., 2020[39]	NSE	Within 6	>54.8 ng/mL	57	0	16	15	26	48.4 (30.2–66.9)	100.0 (86.8–100.0)	0.0 (0.0–13.2)	100.0 (78.2–100.0)	61.9 (45.6–76.4)
	Brain MRI	Within 6	ADC 4.3% of voxels (PV 400)	57	0	18	15	24	45.5 (28.1–63.6)	100.0 (85.8–100.0)	0.0 (0.0–14.2)	100.0 (78.2–100.0)	57.1 (41.0–72.3)
	Brain CT	Within 6	GWR <1.07	58	0	26	6	26	18.8 (7.2–36.4)	100.0 (86.8–100.0)	0.0 (0.0–13.2)	100.0 (54.1–100.0)	50.0 (35.8–64.2)
Bisschops, Lauren L.A. et al., 2011[26]	GCS-M	72	M1–2	103	11	32	35	25	52.2 (39.7–64.6)	69.4 (51.9–83.7)	30.6 (16.3–48.1)	76.1 (61.2–87.4)	43.9 (30.7–57.6)
	SM	Within 168	Clinical jerks' concomitant with EMG artifacts with or without EEG spike correlate	103	4	31	36	32	53.7 (41.1–66.0)	88.9 (73.9–96.9)	11.1 (3.1–26.1)	90.0 (76.3–97.2)	50.8 (37.9–63.6)
	SSEP	>24	Bilateral absence of cortical N20 response	46	0	20	18	8	47.4 (31.0–64.2)	100.0 (63.1–100.0)	0.0 (0.0–36.9)	100.0 (81.5–100.0)	28.6 (13.2–48.7)
	EEG	Within 336	Suppression or burst suppression	27	1	12	11	3	47.8 (26.8–69.4)	75.0 (19.4–99.4)	25.0 (0.6–80.6)	91.7 (61.5–99.8)	20.0 (4.3–48.1)

Note: SM = status myoclonus; PLR = pupillary light reflexes; CR = corneal reflexes; GCS-M = Glasgow Coma Motor Score; EEG = electroencephalography; SSEP = somatosensory evoked potentials; NSE = neuron-specific enolase; ADC = apparent diffusion coefficient; GWR = gray-to-white matter ratio; FP = false positive; FN = false negative; TP = true positive; TN = true negative; FPR = false positive rate; Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; CI = confidence interval; EMG = Electromyography.
*All timing post-ROSC unless mentioned otherwise.

Table 4. Diagnostic accuracy of multimodal combinations reported in each study

Author, Year	Multimodal combination	Timing (hr)*	Threshold used for poor outcome	Number of patients	FP	FN	TP	TN	Sens % (95% CI)	Spec % (95% CI)	FPR % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Kim, Ji Hoon et al., 2020[24]	GCS-M +PLR	72 post-rewarming	GCS-M ≤2 and bilaterally absent PLR	460	0	111	151	198	57.6 (51.4–63.7)	100.0 (98.2–100.0)	0.0 (0.0–1.8)	100.0 (97.6–100.0)	64.1 (58.5–69.4)
	GCS-M +CR	72 post-rewarming	GCS-M ≤2 and bilaterally absent CR	429	4	69	167	189	70.8 (64.9–76.5)	97.9 (94.8–99.4)	2.1 (0.6–5.2)	97.7 (94.1–99.4)	73.3 (67.4–78.6)
	PLR + CR	72 post-rewarming	Both absent bilaterally	447	0	109	144	194	56.9 (50.6–63.1)	100.0 (98.1–100.0)	0.0 (0.0–1.9)	100.0 (97.5–100.0)	64.0 (58.3–69.4)
	GCS-M +PLR + CR	72 post-rewarming	GCS-M ≤2 and both bilaterally absent CR and PLR	447	0	114	135	198	54.2 (47.8–60.5)	100.0 (98.2–100.0)	0.0 (0.0–1.8)	100.0 (97.3–100.0)	63.5 (57.9–68.8)
Zhou, Sonya E. et al., 2019[22]	GCS-M + ≥1 (PLR/CR, SSEP)	≥ 72	-GCS-M ≤2 -Bilaterally absent PLR and CR -SSEP with N20 bilaterally absent	207	0	141	33	33	19.0 (13.4–25.6)	100.0 (89.4–100.0)	0.0 (0.0–10.6)	100.0 (89.4–100.0)	19.0 (13.4–25.6)
	GCS-M + > = 2 (SM, NSE, EEG, CT, MRI)	GCS-M ≥ 72 SM ≤48 NSE 48–72 EEG >24 Brain CT ≤ 24 Brain MRI 48–120	GCS-M ≤2 Myoclonic jerks >30 min NSE >33 ug/L Unreactive burst suppression or status epilepticus Diffuse hypoxic-ischemic brain injury on CT or MRI	207	0	126	48	33	27.6 (21.1–34.9)	100.0 (89.4–100.0)	0 (0.0–10.6)	100.0 (92.6–100.0)	20.8 (14.7–27.9)
Bongiovanni Filippo et al., 2020[20]	≥1 (PLR/CR, SSEP) OR ≥ 2 (SM, NSE, EEG, CT/MRI)	PLR 24–72 CR 24–72 SSEP 24–72 SM ≤ 48 NSE 24–48 EEG 48 CT & MRI 24–72	Bilaterally absent Bilaterally absent N20 bilaterally absent Status myoclonus (no definition) Peak NSE >75 mcg/L Unreactive burst suppression or status epilepticus Diffuse anoxic brain injury	485	0	118	155	212	56.8 (50.7–62.7)	100.0 (98.3–100.0)	0.0 (0.0–1.7)	100.0 (97.6–100.0)	64.2 (58.8–69.4)
Moseby-Knappe Marion et al., 2020[21]	≥ 2 (PLR/CR, SSEP, NSE, EEG, CT, MRI, SM)	PLR/CR ≥ 108 SSEP 84–108 NSE 48 and/or 72 EEG 48–72 CT 10 (2–81) MRI 214 (147–310) SM ≥ 48	Both bilaterally absent Bilaterally absent N20 potentials on short latency ≥ 48 pg/mL at 48 h and/or ≥ 38 pg/mL at 72 h Unreactive burst suppression or unreactive status epilepticus (abundant rhythmic/periodic discharges) Visually evaluated generalized edema seen as a reduced differentiation between gray and white matter Presence of generalized edema Status myoclonus >30 min	585	0	164	102	319	38.3 (32.5–44.5)	100.0 (98.9–100.0)	0.0 (0.0–1.1)	100.0 (96.4–100.0)	66.0 (61.6–70.3)
Oddo, Mauro et al., 2018[36]	Pupillometry (NPi) + SSEP	NPi 48–72 SSEP 48–72	NPi ≤2 Bilaterally absent N20	188	0	52	72	64	58.1 (48.9–66.9)	100.0 (94.4–100.0)	0.0 (0.0–5.6)	100.0 (95.0–100.0)	55.2 (45.7–64.4)

Table 4. Diagnostic accuracy of multimodal combinations reported in each study (*Continued*)

Author, Year	Multimodal combination	Timing (hr)*	Threshold used for poor outcome	Number of patients	FP	FN	TP	TN	Sens % (95% CI)	Spec % (95% CI)	FPR % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Pouplet, Caroline et al., 2022[27]	GCS-M + ≥ 2 (PLR/CR, SSEP, SM, NSE, EEG, CT/MRI)	GCS-M ≥ 72 PLR/CR ≥72 SSEP ≥24 SM ≤ 72 NSE 48 and/or 72 EEG>24 CT/MRI ≤ 72/48–168	GCS-M ≤3 Both bilaterally absent Bilaterally absent N20 Continuous and generalized myoclonus persisting ≥30 min >60 µg/L Highly malignant: suppressed background ± periodic discharges or burst suppression Diffuse anoxic brain injury	16	0	4	10	2	71.4 (41.9–91.6)	100.0 (15.8–100.0)	0.0 (0.0–84.2)	100.0 (69.2–100.0)	33.3 (4.3–77.7)
Roger, Claire et al., 2015[25]	GCS-M +PLR	72	GCS-M <3 Bilaterally absent PLR	52	1	15	15	21	50.0 (31.3–68.7)	95.5 (77.2–99.9)	4.5 (0.1–22.8)	93.8 (69.8–99.8)	58.3 (40.8–74.5)
Scarpino, Maenia et al., 2021[37]	≥2 (PLR, SSEP, CT, EEG, SM)	PLR 72 SSEP 72 EEG 72 Brain CT ≤ 24 SM ≤ 48	Bilaterally absent Absent N20 wave on one side, pathological N20 wave on the other side Malignant EEG: isoelectric, suppression or burst suppression (ACNS) Diffuse anoxic injury (GWR <1.21) Continuous and generalized myoclonic jerks persisting for at least 30 min	210	0	76	88	46	53.7 (45.7–61.5)	100.0 (92.3–100.0)	0.0 (0.0–7.7)	100.0 (95.9–100.0)	37.7 (29.1–46.9)
Ben-Hamouda, Nawfel et al., 2022[38]	≥2 (PLR, SSEP, EEG, NSE, SM)	PLR 72 SSEP >24 EEG 36–72 NSE within 48 SM <72	Absent bilaterally Bilaterally absent N20 Highly malignant (suppressed background with or without repetitive epileptiform discharges and burst suppression with or without discharges) Highest NSE level>60 mcg/L Present (no specific definition given)	399	1	130	115	153	46.9 (40.6–53.4)	99.4 (96.4–100.0)	0.6 (0.0–3.6)	99.1 (95.3–100.0)	54.1 (48.1–60.0)
Youn, Chun Song et al., 2022[28]	GCS-M + ≥2 (PLR/CR, SSEP, EEG, NSE, CT, MRI)	GCS-M ≥ 72 PLR/CR ≥ 72 SSEP ≥24 EEG >24 NSE 48 and/or 72 CT ≤72 MRI 48–168	GCS-M ≤3 Both bilaterally absent Bilaterally absent N20 Highly malignant: suppressed background, suppressed background with continuous periodic discharges and burst suppression background >60 mcg/L Poor CT: Generalized edema Poor MRI: Generalized edema	589	0	211	319	59	60.2 (55.9–64.4)	100.0 (93.9–100.0)	0.0 (0.0–6.1)	100.0 (98.9–100.0)	21.9 (17.1–27.3)
Son, Seung Ha et al., 2020[39]	MRI + NSE	Within 6	NSE >54.8 ng/mL ADC 4.3% of voxels (PV 400)	56	0	16	16	24	50.0 (31.9–68.1)	100.0 (85.8–100.0)	0.0 (0.0–14.2)	100.0 (79.4–100.0)	60.0 (43.4–75.1)

(*Continued*)

Table 4. Diagnostic accuracy of multimodal combinations reported in each study (*Continued*)

Author, Year	Multimodal combination	Timing (hr)*	Threshold used for poor outcome	Number of patients	FP	FN	TP	TN	Sens % (95% CI)	Spec % (95% CI)	FPR % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
	CT + NSE	Within 6	NSE >54.8 ng/mL GWR <1.07	56	0	16	16	24	50.0 (31.9–68.1)	100.0 (85.8–100.0)	0.0 (0.0–14.2)	100.0 (79.4–100.0)	60.0 (43.3–75.1)
Bisschops, Lauren L.A, et al., 2011[26]	GCS-M + PLR + CR	72	M1–2 Both bilaterally absent PLR and CR	103	0	57	10	36	14.9 (7.4–25.7)	100.0 (90.3–100.0)	0.0 (0.0–9.7)	100.0 (69.2–100.0)	38.7 (28.8–49.4)

Note: SM = status myoclonus; PLR= pupillary light reflexes; CR = corneal reflexes; GCS-M = Glasgow Coma Motor Score; EEG = electroencephalography; SSEP = somatosensory evoked potentials; NSE = neuron-specific enolase; ADC = apparent diffusion coefficient; GWR = gray-to-white matter ratio; FP = false positive; FN = false negative; TP = true positive; TN = true negative; FPR = false positive rate; Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; CI = confidence interval.
*All timing post-ROSC unless mentioned otherwise.

absent N20 on SSEP at 48–72 h post-ROSC[36] and NSE >54.8 ng/mL and either abnormal brain CT or brain MRI within 6 h.[39] All combinations excluding GCS-M, unless part of the ERC-ESCIM algorithm, had specificity greater than 99% (FPR <1%),[20–22,24,27,28,36–39] while most of them had sensitivity >50%.[20,24,27,28,36,37,39]

Comparison of the diagnostic accuracy of multimodal versus unimodal testing

Figures 2 and 3 illustrate the comparison of the FPR and sensitivity between multimodal and unimodal data for all included studies. A meta-analysis was not possible for several reasons. We noted significant publication bias in our funnel plots, Egger's[35] and Begg's test[34] (Figures S1 and S2). More importantly, each multimodal combination of tests used different combinations of single tests assessed at various time points after ROSC, with different thresholds for each single test. Moreover, the neurological outcomes were not assessed at the same time point in all the included studies. For these reasons, a summary estimate of specificity and sensitivity for unimodal and multimodal data could not be calculated. In addition, a key assumption of meta-analyses is that estimates are mutually independent,[41] which was not met with our data. Lastly, there was a significant amount of heterogeneity in the collected data that varied between 0% and 96% when measured.

Discussion

This systematic review summarizes the accuracy of both multimodal and unimodal approaches in predicting poor neurological outcomes post-cardiac arrest. While a meta-analysis was not possible, review of the reported data suggests that a multimodal approach, regardless of the combination of modalities, may increase specificity and sensitivity when predicting poor outcomes compared to a unimodal approach. To our knowledge, this is the first systematic review comparing multimodal and unimodal approaches in neuroprognostication of post-cardiac arrest patients. Previous studies assessed multiple tests used as individual modalities but did not compare diagnostic accuracy between multimodal and unimodal approaches as a systematic review.[42–45]

Accurate neuroprognostication is paramount to avoid inappropriate WLSM but also to circumvent prolonged, invasive and costly therapies that could perpetuate patient and family suffering when there is no realistic chance of favorable recovery.[46–48] Despite the profound impact of WLSM decisions, there is a lack of consensus regarding an acceptable FPR in the determination of prognosis post-cardiac arrest. Most guidelines include modalities with an FPR (or the upper level of the confidence interval) ≤5%.[8–11] However, one recently published national survey suggests that providers prefer an FPR <1% when predicting a poor prognosis and recommending WLSM.[49] An international survey suggested that many even prefer an FPR <0.1%.[50] While several factors are integrated into shared decision-making about patients' goals of care, prognostic certainty forms the foundation for these discussions. Studies suggest that uncertainty, especially when suppressed or ignored, can have a negative impact on families and healthcare providers.[51] Up to 70% of physicians report feeling some level of distress when determining post-arrest prognosis, much of which stems from managing uncertainty.[49]

While many studies reported FPRs of 0% for individual modalities recommended in recent guidelines, others reported FPRs as high as 6% for bilaterally absent PLR or CR,[22,24] 4% for status myoclonus[22,27] and up to 31% for GCS-M ≤2.[26] The highest FPR reported for EEG, SSEP, CT, MRI and NSE used in isolation

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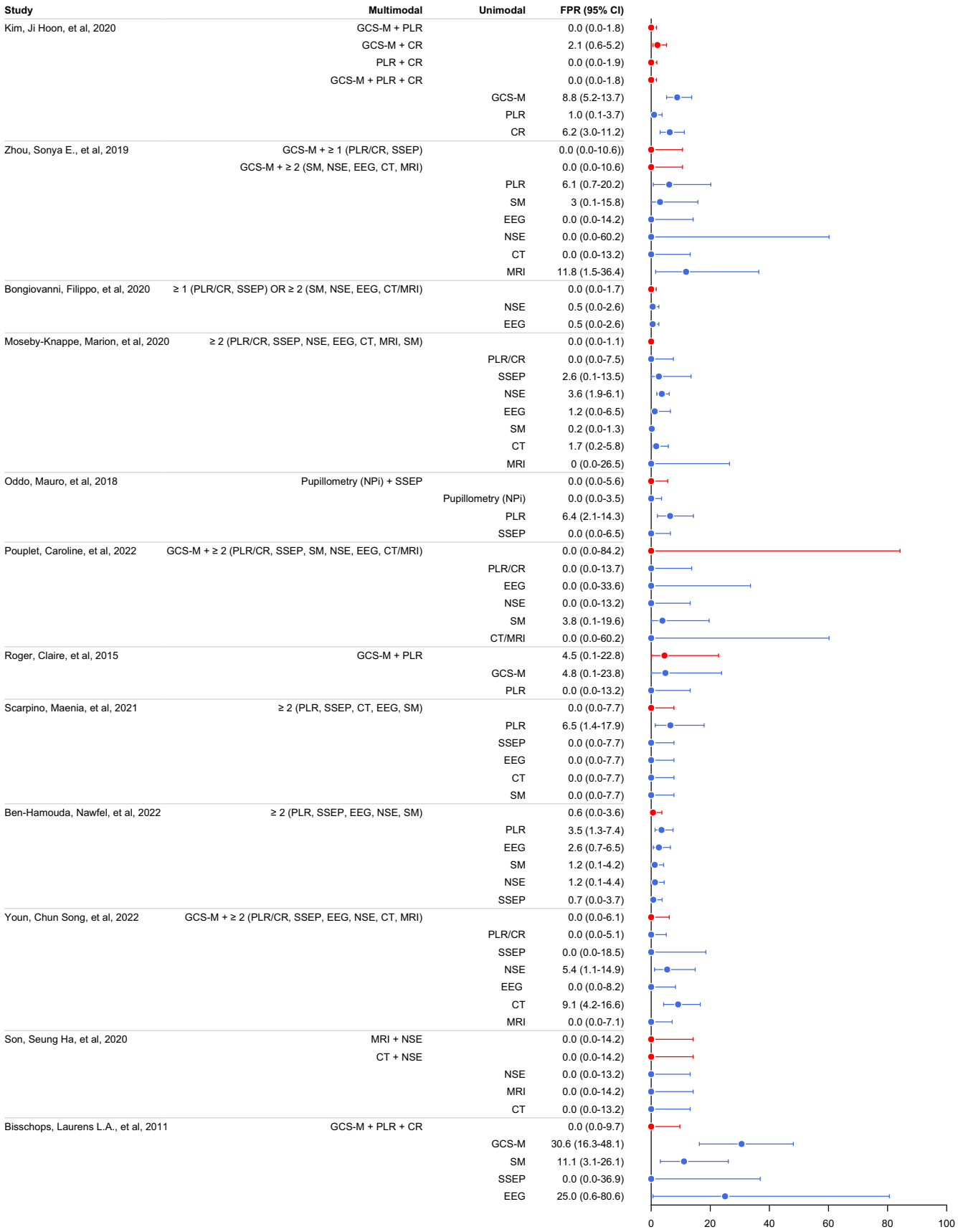

Figure 2. Comparison of the false positive rate of multimodal versus unimodal data from included studies.

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Study	Multimodal	Unimodal	Sensitivity (95% CI)
Kim, Ji Hoon, et al, 2020	GCS-M + PLR		57.6 (51.4-63.7)
	GCS-M + CR		70.8 (64.9-76.5)
	PLR + CR		56.9 (50.6-63.1)
	GCS-M + PLR + CR		54.2 (47.8-60.5)
		GCS-M	88.4 (84.0-92.0)
		PLR	60.4 (54.3-66.3)
		CR	74.4 (68.3-79.8)
Zhou, Sonya E., et al, 2019	GCS-M + ≥ 1 (PLR/CR, SSEP)		19.0 (13.4-25.6)
	GCS-M + ≥ 2 (SM, NSE, EEG, CT, MRI)		27.6 (21.1-34.9)
		PLR	28.3 (21.7-35.7)
		SM	30.6 (24.2-37.6)
		EEG	13.9 (9.1-19.9)
		NSE	50.0 (31.3-68.7)
		CT	14.3 (9.2-20.8)
		MRI	74.7 (63.6-83.8)
Bongiovanni, Filippo, et al, 2020	≥ 1 (PLR/CR, SSEP) OR ≥ 2 (SM, NSE, EEG, CT/MRI)		56.8 (50.7-62.7)
		NSE	13.2 (8.1-19.8)
		EEG	18.1 (12.1-25.3)
Moseby-Knappe, Marion, et al, 2020	≥ 2 (PLR/CR, SSEP, NSE, EEG, CT, MRI, SM)		38.3 (32.5-44.5)
		PLR/CR	20.1 (15.3-25.5)
		SSEP	45.3 (37.5-53.4)
		NSE	60.2 (54.5-65.7)
		EEG	38.0 (31.6-44.8)
		SM	6.9 (4.8-9.5)
		CT	32.3 (26.4-38.7)
		MRI	13.0 (2.8-33.6)
Oddo, Mauro, et al, 2018	Pupillometry (NPi) + SSEP		58.1 (48.9-66.9)
		Pupillometry (NPi)	16.8 (11.4-23.3)
		PLR	18.0 (11.7-25.7)
		SSEP	48.1 (39.4-56.9)
Pouplet, Caroline, et al, 2022	GCS-M + ≥ 2 (PLR/CR, SSEP, SM, NSE, EEG, CT/MRI)		71.4 (41.9-91.6)
		PLR/CR	5.3 (0.1-26.0)
		EEG	47.4 (24.4-71.1)
		NSE	54.5 (32.2-75.6)
		SM	26.1 (10.2-48.4)
		CT/MRI	37.5 (8.5-75.5)
Roger, Claire, et al, 2015	GCS-M + PLR		50.0 (31.3-68.7)
		GCS-M	94.0 (83.5-98.7)
		PLR	51.4 (34.0-68.6)
Scarpino, Maenia, et al, 2021	≥ 2 (PLR, SSEP, CT, EEG, SM)		53.7 (45.7-61.5)
		PLR	48.8 (40.9-56.7)
		SSEP	51.8 (43.9-59.7)
		EEG	47.3 (39.5-55.2)
		CT	34.8 (27.5-42.6)
		SM	2.4 (0.7-6.1)
Ben-Hamouda, Nawfel, et al, 2022	≥ 2 (PLR, SSEP, EEG, NSE, SM)		46.9 (40.6-53.4)
		PLR	32.7 (27.1-38.7)
		EEG	30.6 (24.8-36.8)
		SM	22.8 (17.9-28.4)
		NSE	42.5 (36.3-48.9)
		SSEP	39.1 (32.9-45.5)
Youn, Chun Song, et al, 2022	GCS-M + ≥ 2 (PLR/CR, SSEP, EEG, NSE, CT, MRI)		60.2 (55.9-64.4)
		PLR/CR	62.9 (58.2-67.4)
		SSEP	72.7 (64.3-80.1)
		NSE	78.8 (73.8-83.3)
		EEG	59.2 (52.2-66.0)
		CT	32.8 (28.7-37.1)
		MRI	78.0 (72.7-82.7)
Son, Seung Ha, et al, 2020	MRI + NSE		50.0 (31.9-68.1)
	CT + NSE		50.0 (31.9-68.1)
		NSE	48.4 (30.2-66.9)
		MRI	45.5 (28.1-63.6)
		CT	18.8 (7.2-36.4)
Bisschops, Laurens L.A., et al, 2011	GCS-M + PLR + CR		14.9 (7.4-25.7)
		GCS-M	52.2 (39.7-64.6)
		SM	53.7 (41.1-66.0)
		SSEP	47.4 (31.0-64.2)
		EEG	47.8 (26.8-69.4)

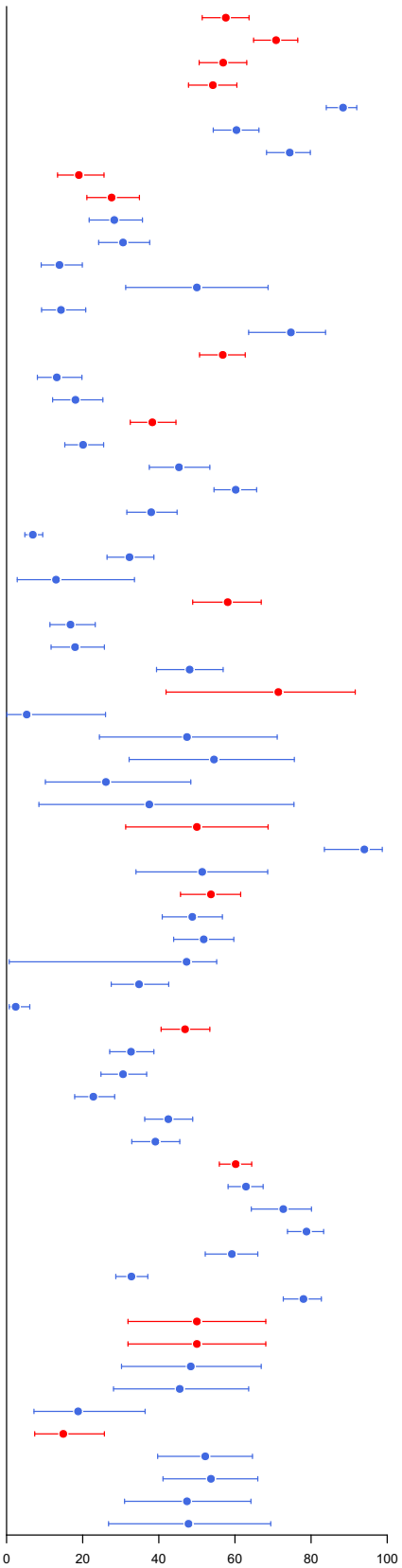

Figure 3. Comparison of the sensitivity of multimodal versus unimodal data from included studies.

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was 25%,[26] 3%,[21] 9%,[28] 12%[22] and 5%,[28] respectively. No single test is perfect. The variability of FPRs likely results from several factors, including those inherent to observational studies, such as the inability to control for confounding factors (variably reported in studies), inter- and intra-observer variability when reporting test results and characteristics of each modality, such as spatial and temporal resolution. Providers should also be mindful that positive verification bias ("self-fulfilling prophecy") that is inherent in many studies may falsely lower the reported FPRs of individual modalities, though findings in our systematic review were concordant in studies where WLSM was not pursued.

The European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM) published guidelines for neuroprognostication after cardiac arrest in 2014 [52] and 2015[23] comprised of a four-step algorithm. This multimodal approach has been tested retrospectively using data from the TTM trial[21] and predicted poor neurological outcome (CPC 3–5) with a specificity of 100% but failed to identify approximately 60% of patients with poor neurological outcomes.[21] The more contemporary ERC/ESICM,[9] Neurocritical Care Society,[11] American Heart Association[10] guidelines and Canadian position statement[8] all recommend a multimodal approach, albeit based on low-quality evidence. Recommendations are based on the assumption that a multimodal approach leads to improved FPR and sensitivity, as the chances of discovering findings indicative of a poor prognosis are increased when more tests are performed. Several questions remain, however, including the ideal number and combination of modalities required in a multimodal approach and whether that approach improves specificity and/or sensitivity in predicting poor outcomes.

One limitation of this review includes the publication bias of included studies as demonstrated by our funnel plots, Egger's and Begg's tests. Many of the included studies also had a moderate to high degree of bias. This was unfortunately unavoidable, since most studies were retrospective and observational in nature, with inconsistency in reporting confounders, such as the effects of sedation, opioids and profound physiologic or metabolic disturbance, all of which are important considerations for neuroprognostication. Lastly, heterogeneity[53] between studies was high and was an important reason why conducting a meta-analysis was not possible. The included studies used similar but distinct combinations of tests, with variable diagnostic thresholds and timing, as well as variation in study size, proportion of patients with shockable rhythms, and different cardiac arrest settings, thereby precluding calculation of summary estimates. TTM was utilized in all studies, although not in all patients,[22,37] with variable temperature goals and durations (Table S4). TTM is known to affect the ideal timing and accuracy of modalities used in neuroprognostication.[54,55] While the TTM literature continues to evolve, care providers should be mindful of the possible effects TTM may have on diagnostic tests.

Despite these limitations, this systematic review utilized established methodology and a pre-registered protocol. While unanswered questions remain, these rigorous methods and selection process are emulating contemporary recommendations in neuroprognostication, which in turn increases the strength of our conclusion.

Conclusions

A multimodal approach to neuroprognostication aimed at identifying concordant findings in two or more modalities recommended in contemporary guidelines to predict a poor prognosis is feasible and may improve the FPR and sensitivity compared to an approach that utilizes the findings of individual modalities. More research is required to establish the ideal number and combination of modalities, as well as whether modalities not yet recommended in guidelines may also be of benefit in a multimodal approach.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2025.10112.

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CB: conceptualization, methodology, investigation.
AS: conceptualization, software, formal analysis.
AK: conceptualization, methodology, writing – review and editing.
JK: conceptualization, methodology, investigation, supervision, writing – review and editing.

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