NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Quality in Sport. eISSN 2450-3118.

Journal Home Page
https://apcz.umk.pl/QS/index

KOWALEWSKI, Piotr, KUCHTA, Eliza, KOWALCZYK, Natalia, WRZOSEK, Kacper, DUDEK, Karolina, BŁAŻUKIEWICZ, Jan, CIUPAK, Klaudia, GARBACKI, Klaudiusz, POPEK, Lena, DUDEK, Bartosz, and PIECEWICZ-SZCZĘSNA, Halina. Targeted Temperature Management Post-Cardiac Arrest: Shifting Paradigms from Hypothermia to Strict Normothermia and its Impact on Neurological Prognostication. Quality in Sport. 2026;55:71174. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.55.71174

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 22.04.2026. Revised: 27.04.2026. Accepted: 3.05.2026. Published: 10.05.2026.

Targeted Temperature Management Post-Cardiac Arrest: Shifting Paradigms from Hypothermia to Strict Normothermia and its Impact on Neurological Prognostication

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Abstract

Background. Cardiac arrest (CA) remains a major global health challenge with high risk of severe neurological impairment. Post-cardiac arrest syndrome (PCAS), particularly hypoxic-ischemic brain injury, drives mortality and long-term disability. Targeted temperature management (TTM), traditionally a neuroprotective cornerstone, is currently being re-evaluated.

Aim. To analyze current evidence on post-CA temperature management, focusing on the shift from therapeutic hypothermia to strict normothermia and its implications for neurological prognostication.

Materials and methods. This narrative review synthesizes 30 peer-reviewed publications, including randomized trials, systematic reviews, and international guidelines (ERC, ESICM, NCS). It evaluates PCAS pathophysiology, hypothermia versus normothermia outcomes, technical TTM implementation, and multimodal neuroprognostication.

Results. Recent high-quality evidence shows no significant benefit of routine therapeutic hypothermia (32–34°C) over strict normothermia in improving survival or neurological outcomes. Guidelines now emphasize active fever prevention (≤37.5°C) using precise control systems. While TTM modulates systemic inflammation (e.g., IL-6), this does not independently lower mortality. Neurological prognostication requires a delayed, multimodal approach integrating clinical assessments and biomarkers like neuron-specific enolase (NSE), while accounting for confounders.

Conclusions. Post-CA management has shifted toward individualized, precision-based care, with strict normothermia and active fever prevention as the recommended standard. Accurate neuroprognostication necessitates adherence to guideline-directed timing and multimodal strategies. Future research should identify specific subgroups benefiting from hypothermia and develop adjunctive therapies.

Keywords: cardiac arrest; targeted temperature management; normothermia; hypothermia; neuroprognostication; post-cardiac arrest syndrome

1. Introduction

CA represents one of the most critical public health challenges worldwide, accounting for a substantial proportion of cardiovascular-related deaths [1, 2]. Despite continuous advancements in prehospital emergency care, elaborate post-resuscitation algorithms, and improvements in the "chain of survival," overall survival rates to hospital discharge remain remarkably low [1, 3]. Current clinical observations indicate that achieving survival with intact neurology after an out-of-hospital cardiac arrest (OHCA) remains a major challenge, with many patients failing to recover meaningful brain function despite successful initial resuscitation [4].

The primary determinant of mortality and long-term severe disability in comatose survivors who successfully achieve the return of spontaneous circulation (ROSC) is the development of PCAS [5, 6]. PCAS is a highly complex pathophysiological entity that encompasses four distinct components: post-cardiac arrest brain injury (PCABI), myocardial dysfunction, a systemic ischemia-reperfusion response, and the persistent precipitating pathology that caused the arrest [5, 6]. Among these, cerebral injury resulting from the initial hypoxia and subsequent reperfusion is the most devastating complication, serving as the main cause of death in the acute post-resuscitation phase and the primary driver of long-term disability among survivors [3, 6].

1.1. Pathophysiology of Post-Cardiac Arrest Syndrome (PCAS)

PCAS is a highly complex, multi-organ clinical entity that begins immediately following the ROSC. According to the current literature, it comprises four distinct but interrelated pathophysiological components: PCABI, post-cardiac arrest myocardial dysfunction, a systemic ischemia-reperfusion response, and the persistent precipitating pathology that caused the initial arrest [5].

Cerebral injury remains the most devastating and complex complication, determining the ultimate functional prognosis. It develops sequentially in two main phases: a primary ischemic injury and a secondary reperfusion injury [6]. The primary injury occurs during the absolute cessation of blood flow, leading to an of this inflammation by highlighting the critical involvement of the gut-brain axis [7]. Ischemia during CA heavily damages the intimmediate depletion of cerebral oxygen and adenosine triphosphate (ATP) reserves. This rapid energy failure results in the loss of neuronal membrane potential, a significant intracellular influx of calcium ions, and the excitotoxic release of neurotransmitters, particularly glutamate [6].

Upon successful ROSC, the secondary injury phase begins. Reperfusion of the ischemic brain tissue generates severe oxidative stress through the production of reactive oxygen species

(ROS) and induces significant mitochondrial dysfunction, both of which serve as primary triggers for neuronal apoptosis [6]. This secondary phase is further characterized by an extensive neuroinflammatory cascade. Recent literature has significantly expanded the understanding estinal barrier, leading to gut dysbiosis. As a result, gut-derived macrophages migrate and infiltrate the injured brain, actively driving secondary brain injury through pro-inflammatory Triggering Receptor Expressed on Myeloid Cells (TREM-1) signaling [7].

Concurrently, the systemic ischemia-reperfusion response triggers the substantial release of major systemic inflammatory cytokines, such as IL-6 [8]. This systemic hyperinflammation typically manifests as a severe "sepsis-like" syndrome, characterized by generalized vasoplegia, endothelial damage, and microcirculatory failure, which continuously threatens the viability of the recovering brain [5, 6].

1.2. The Biological Rationale for Temperature Management

The intentional modulation of core body temperature has been the cornerstone of neuroprotective strategies following CA for decades [3, 9]. The physiological hypothesis supporting therapeutic hypothermia (traditionally defined as cooling to 32°C–34°C) rests on its robust ability to simultaneously suppress multiple, converging pathways of secondary brain injury triggered during reperfusion [3, 6].

Specifically, inducing hypothermia significantly reduces the cerebral metabolic rate for oxygen. This artificially diminished metabolic demand delays the critical depletion of cellular energy stores (ATP) and actively decreases the excessive extracellular accumulation of excitotoxic neurotransmitters, particularly glutamate [3, 5]. Lower core temperatures stabilize lipid bilayers and neuronal cell membranes, successfully mitigating the detrimental intracellular influx of calcium. Preventing this calcium overload is critical, as it is the primary driver of mitochondrial failure and subsequent delayed neuronal apoptosis [5, 6].

Beyond direct structural and metabolic brain protection, hypothermia profoundly affects the immune cascade. As demonstrated in extensive systematic reviews of preclinical animal models, temperature modulation directly mitigates generalized ischemia-reperfusion injury at the cellular level [20]. In human clinical observations, the application of TTM has been shown to blunt the severe systemic inflammatory response induced by PCAS. It achieves this by actively inhibiting the synthesis and hyperacute release of major pro-inflammatory cytokines, most notably IL-6, which is otherwise strongly correlated with exacerbated secondary brain injury and higher overall mortality [8, 11].

1.3. Historical Evolution and the Paradigm Shift

The modern era of temperature management in post-resuscitation care was initiated following two foundational randomized clinical trials published in 2002 (the Bernard and HACA trials). These early studies reported improved overall survival and favorable neurological outcomes for comatose patients treated with mild induced hypothermia (typically targeting 32°C to 34°C) compared to standard care without temperature control [3, 12]. These initial findings prompted international resuscitation councils to strongly recommend the routine use of therapeutic hypothermia for comatose survivors of OHCA, establishing it as a global standard of care for over a decade [1, 3].

However, as general intensive care and protocolized post-resuscitation algorithms rapidly improved, the certainty of these specific neuroprotective benefits was intensely scrutinized. The evolution of modern care protocols led to the landmark TTM trial in 2013, which found no significant difference in outcomes between cooling to 33°C versus 36°C [1]. This was subsequently followed by the definitive TTM 2 trial in 2021, which comprehensively demonstrated that targeted hypothermia at 33°C did not confer any survival or neurological advantage over targeted strict normothermia (defined as maintaining a core temperature of ≤37.5°C and actively treating any fever) [1, 13].

These clinical findings have triggered a major paradigm shift in resuscitation science, culminating in radically updated international guidelines. Most notably, the recent consensus guidelines from the ERC and the ESICM have formally shifted the recommendation away from mandatory deep cooling [14, 15]. The current standard of care now strongly prioritizes a strategy of strict, active normothermia. This involves continuous core temperature monitoring and the aggressive, device-assisted prevention of fever for at least 72 hours post-ROSC, fundamentally altering the clinical approach to mitigating secondary brain injury [14, 15].

2. Methods Review

This narrative medical review is based on an analysis of 30 peer-reviewed scientific articles to evaluate current strategies in PCAS.

Selection Criteria: All included articles were published in peer-reviewed journals. The source pool encompasses high-certainty systematic reviews, prominently including a comprehensive Cochrane review assessing neuroprotection (Arrich, Schütz et al.) [10], as well as recent meta-analyses evaluating the minimization of secondary brain injury (Seixas et al.) [9]. The analysis heavily integrates official international clinical guidelines to ensure the highest standard of current practice; these include the ERC 2025 Adult Advanced Life Support

guidelines [15], the joint ERC-ESICM consensus on temperature control [14], and the NCS guidelines for neuroprognostication [16].

In addition, the database incorporates data from randomized clinical trial sub-studies (e.g., the ISOCRATE and HYPERION analyses) [11, 17], large-scale prospective and retrospective observational studies utilizing national registries (e.g., TIMECARD in Taiwan, KORHN-PRO in South Korea) [5, 18], and contemporary expert reviews addressing the controversies of the landmark TTM 2 trial to provide critical clinical perspectives [13].

Method of Analysis: Extracted data were systematically categorized into three main analytical domains:

1. Pathophysiology and Comparative Clinical Outcomes: Evaluating the therapeutic shift from hypothermia to normothermia, while exploring novel pathophysiological pathways of secondary brain injury, such as the gut-brain axis.
2. Technical Implementation of TTM: Assessing the practical application of temperature control, including prehospital cooling viability, device precision (intravascular versus surface cooling), physiological shivering management, and the modulation of systemic inflammation (e.g., rewarming rates and IL-6 clearance) [11].
3. Multimodal Neurological Prognostication: Focusing on guideline-directed assessment timings, biomarker kinetics, individualized threshold cutoffs for predicting outcomes, and critical laboratory limitations, such as the impact of sample hemolysis on NSE measurements [16, 19].

3. Results and Current Evidence

3.1. Comparison of Hypothermia Versus Normothermia

The primary goal of post-cardiac arrest care is mitigating anoxic brain injury. While a comprehensive meta-analysis of animal models by Arrich, Herkner et al. [20] demonstrated that conventional TTM between 32°C and 36°C significantly improved neurological outcomes and reduced mortality in controlled laboratory settings, translating these neuroprotective benefits to modern human intensive care has proven challenging.

Contemporary clinical evidence, comprehensively evaluated in the latest Cochrane Systematic Review by Arrich, Schütz et al. [10], alongside analyses by Seixas et al. [9] and Lüsebrink et al. [1], indicates that temperature control targeting 32°C to 34°C does not result in a statistically significant improvement in overall survival or favorable neurological outcomes when compared to strict normothermia combined with early, active fever prevention. The latest

consensus guidelines from the ERC and the ESICM robustly support the shift away from routine deep cooling. Current protocols formally recommend continuous temperature monitoring and the active prevention of fever (maintaining core temperature ≤37.5°C) for all comatose survivors [14, 15].

However, registry data and trial sub-analyses emphasize that the efficacy of TTM protocols may vary significantly depending on the clinical context. For instance, the TIMECARD registry analysis by Chien et al. [21] highlighted significant outcome differences between OHCA and in-hospital cardiac arrest (IHCA) patients. While TTM is applied to both, demographic variations, the etiology of the arrest, and initial hemodynamic stability heavily dictate the ultimate neurological status. Also, a post hoc analysis of the HYPERION trial by Ziriat et al. [17], which investigated patients with mild-to-moderate post-resuscitation shock following non-shockable CA, highlighted the complex interplay between targeted hypothermia, hemodynamics, and vasopressor support, suggesting that cooling strategies may have divergent physiological impacts based on shock severity.

Because of these clinical nuances, experts such as Skrifvars and Abella argue that completely abandoning deep cooling may be premature. They hypothesize that specific, moderately injured patient subgroups might still experience targeted neuroprotective benefits that are currently diluted and masked in large, heterogeneous "all-comer" clinical mega-trials [13].

3.2. Modulation of the Systemic Inflammatory Response

PCAS inevitably triggers a massive systemic inflammatory cascade. In this context, IL-6 serves as a paramount pro-inflammatory marker, with elevated circulating levels strongly correlated with severe brain injury, hemodynamic instability, and high mortality [8, 22].

A prospective cohort study by Chen et al. directly investigated the effect of TTM on plasma IL-6 concentrations. The researchers found that active cooling effectively blunts the hyperacute release of this cytokine, demonstrating significantly lower IL-6 levels at 24 and 48 hours post-arrest compared to non-TTM patients, which is theorized to mitigate secondary neuroinflammation [8]. However, while TTM successfully modulated the systemic cytokine surge, this singular anti-inflammatory effect did not independently translate into drastically lower 90-day mortality among the most critically ill cohorts [8].

The management of temperature transition—specifically the rewarming phase following targeted hypothermia—has been investigated for its potential to trigger a secondary inflammatory rebound (often termed "rewarming shock"). The ISOCRATE pilot randomized

controlled trial, conducted by Lascarrou et al., evaluated whether a slower rewarming rate (0.25 °C/h) could better suppress systemic inflammation compared to a standard rewarming rate (0.5 °C/h) in patients treated at 33°C. The trial demonstrated no significant difference in serum IL-6 levels between the two groups at 24 to 48 hours after reaching the target temperature. This indicates that artificially slowing the rewarming speed does not meaningfully attenuate the systemic inflammatory response [11].

Given the limitations of thermal modulation alone in entirely abolishing inflammation, pharmacological adjuncts are being actively explored. A sub-study of the STEROHCA trial by Obling et al. demonstrated that the early administration of high-dose prehospital glucocorticoids (such as methylprednisolone) significantly decreased circulating IL-6 and C-reactive protein (CRP) levels over the first three days of admission. This suggests that targeted pharmacological interventions can successfully and rapidly suppress the PCAS-induced inflammatory storm, potentially serving as a powerful complementary approach to physical temperature management [22].

3.3. Technical Implementation: Equipment and Precision

Transitioning the clinical target from deep hypothermia to strict normothermia does not eliminate the need for advanced technical equipment. Passively managing temperature frequently results in deleterious "rebound fever," which drastically increases cerebral metabolism and worsens secondary ischemic injury [3, 14]. Current ERC-ESICM guidelines mandate the use of active, device-driven temperature feedback systems (TFS) to continuously monitor and strictly maintain core temperature (≤37.5°C) [14].

The implementation of these systems also involves critical decisions regarding the timing and modality of cooling. Historically, prehospital cooling was theorized to maximize neuroprotection by initiating temperature drops immediately after the arrest. However, the SPARC randomized controlled trial by Scales et al. demonstrated that conventional prehospital cooling (utilizing cold saline and ice packs) did not significantly improve the proportion of patients achieving successful targeted temperature management or long-term survival, highlighting substantial logistical challenges in the field [23]. Conversely, the concept of "ultrafast" hypothermia is currently being explored. The ongoing PRINCESS 2 trial (Dillenbeck et al.) aims to determine whether extremely rapid, trans-nasal evaporative intra-arrest cooling can specifically improve complete functional neurological recovery, hypothesizing that only ultra-early intervention can halt the initial phases of injury [24].

Once in the intensive care unit, the choice of cooling modality strictly dictates precision. A recent post hoc analysis of the TTM 2 trial by Awad et al. directly compared intravascular cooling (IC) devices with surface-cooling (SFC) systems. The study robustly demonstrated that IC devices provide superior technological performance: they achieve target temperatures significantly faster and are associated with far fewer detrimental fluctuations, remarkably reducing the incidence of both inadvertent overcooling and rebound hyperthermia compared to SFC [25]. Similarly, Huang et al. evaluated different TTM methods in critically ill patients undergoing extracorporeal cardiopulmonary resuscitation (ECPR). They found that advanced closed-loop systems (such as the Hico-variotherm 550) yielded far greater thermoregulatory precision and better biomarker profiles (lower NSE levels) than traditional medical water-circulating cooling blankets [26].

Finally, achieving precise thermoregulation is frequently complicated by patient-specific physiological variables. Ochiai and Otomo identified that demographic factors, specifically patient age and Body Mass Index (BMI), heavily influence cooling dynamics [27]. Patients with higher BMIs or extreme age profiles present distinct thermal resistance, rendering them highly prone to unpredictable temperature deviations and necessitating highly individualized, continuous device monitoring [27].

3.4. Managing Complications: The Shivering Reflex

A significant physiological barrier to the effective implementation of TTM—whether aiming for hypothermia or strict normothermia—is the human shivering reflex. As the core body temperature drops or attempts are made to prevent fever, the body initiates shivering as a compensatory, thermoregulatory defense mechanism [5, 14]. This reflex is highly detrimental to the recovering brain: it generates substantial involuntary heat, drastically increases systemic metabolic and oxygen consumption, and destabilizes hemodynamics, all of which directly threaten to exacerbate secondary ischemic brain injury [5, 14].

To counteract this, modern post-resuscitation algorithms mandate aggressive, preemptive shivering suppression. Huynh et al. investigated this clinical challenge and demonstrated that implementing a formalized, multi-tiered pharmacologic antishivering protocol dramatically reduces the incidence of shivering events during both the induction and maintenance phases of temperature control [28]. This standardized protocol utilizes a step-wise approach: it initiates with baseline and enteral agents (such as magnesium sulfate and buspirone) and rapidly escalates to continuous intravenous infusions of targeted sedatives (e.g., dexmedetomidine or propofol) and analgesics (e.g., fentanyl) [28].

Protocolized care models, such as those detailed by Chen et al. and the consensus ERC-ESICM guidelines, emphasize that if deep sedation and analgesia are insufficient to control severe shivering, the judicious application of neuromuscular blocking agents (NMBAs) becomes a necessary, definitive step [5, 14]. Paralyzing the patient effectively arrests the muscular generation of heat. Suppressing shivering through these standardized pharmacological algorithms ensures a faster time to reach the target temperature, prevents dangerous thermal fluctuations, and secures significantly greater hemodynamic stability for the critically ill patient [5, 28].

4. Neurological Prognostication

Accurate neuroprognostication is paramount in the post-resuscitation phase, as it directly guides critical, irreversible decisions regarding the continuation or withdrawal of life-sustaining therapy (WLST). In the modern era, to minimize the risk of falsely predicting a poor outcome, this approach has evolved from relying on isolated clinical signs into a highly regimented, multimodal process [6, 16].

4.1. Timing of Neurological Assessment

A fundamental principle of modern neuroprognostication is the strict avoidance of premature assessment. Official consensus guidelines, including the NCS guidelines and the ERC 2025 update, explicitly mandate that definitive prognostic clinical assessments must not be performed earlier than 72 hours after the ROSC [15, 16]. In certain clinical scenarios, this observation window must be extended even further to account for the phenomenon of "delayed awakening" [6].

This mandatory delay is crucial primarily due to the significant confounding effects of ongoing intensive care interventions. As demonstrated by Huynh et al., maintaining temperature targets and managing the shivering reflex requires continuous, high-dose infusions of sedatives (e.g., propofol, dexmedetomidine) and potent analgesics (e.g., fentanyl) [28]. Protocolized post-cardiac arrest care and temperature modulation itself drastically alter the pharmacokinetics and pharmacodynamics of these medications [5]. Both hypothermia and targeted normothermia, often accompanied by post-resuscitation hepatic or renal dysfunction, significantly prolong the clearance and half-lives of these depressant drugs [5, 16].

Attempting to evaluate clinical markers, such as motor responses or consciousness levels, before these medications have been thoroughly metabolized and cleared from the patient's system is highly hazardous. Premature assessment risks generating a falsely

pessimistic neurological prognosis, which could tragically precipitate the inappropriate withdrawal of life support in patients who might otherwise achieve meaningful functional recovery [6, 16]. Therefore, achieving an objective "off-sedation" baseline at or beyond the 72-hour mark is a non-negotiable prerequisite for accurate prognostication [15, 16].

4.2. Serum Biomarkers: NSE and S100B

To mitigate clinical subjectivity, objective biochemical markers have been formally integrated into modern prognostication algorithms. Ryczek et al. identified NSE and S100B protein as the earliest objective predictors of poor neurological outcome, as their serum concentrations rise significantly within the first few days following hypoxic-ischemic neuronal and glial destruction [29].

According to the latest NCS guidelines, NSE measurements should be performed serially to assess the biomarker's trajectory over time. A consistently high or rising NSE value (e.g., >60 ng/ml) evaluated at 48 to 72 hours post-ROSC is highly specific for predicting a poor neurological outcome [16]. However, the clinical utility of NSE is critically dependent on rigorous laboratory precision. A comprehensive analysis by Babkina et al. highlights significant methodological limitations, most notably the significant confounding effect of sample hemolysis [19]. Because erythrocytes contain high concentrations of NSE, even mild hemolysis during blood collection or processing can lead to falsely elevated serum NSE levels. This artificial spike can misleadingly suggest extensive brain injury, creating a severe risk of inappropriate WLST in patients who might otherwise awaken [19]. Contemporary guidelines, including the ERC 2025 update, categorically mandate that blood samples must be rigorously checked for hemolysis, and all NSE values must be interpreted with caution within a broader clinical context [15].

Also, recent data highlight the necessity of personalizing cutoff thresholds. A prospective multicenter study utilizing the KORHN-PRO registry (Kim YJ et al.) revealed that the optimal neuroprognostication thresholds for NSE differ significantly based on the initial CA rhythm. Patients presenting with non-shockable rhythms exhibit different biomarker kinetics and require distinct prognostic thresholds compared to those with shockable rhythms [18]. Importantly, the clinical utility of these biomarkers has expanded beyond predicting futility. Kim D et al. established that maintaining normal (low) NSE values over the first few days post-arrest serves as a robust, independent predictor of a favorable neurological outcome and successful awakening [30]. Therefore, to ensure prognostic accuracy, all biomarker data must be synthesized within a regimented, multimodal framework [15, 16].

4.3. Individualizing NSE Thresholds Based on Arrest Rhythm

Defining the exact NSE cutoff threshold for predicting a definitively poor neurological outcome - and consequently justifying the WLST - is highly controversial. Because the consequence of a false prediction is death, international guidelines mandate that any chosen threshold must carry a false-positive rate (FPR) of zero, or strictly <1% [16].

Recent evidence underscores that a "one-size-fits-all" approach to these biomarker cutoffs is clinically flawed and potentially hazardous. A large-scale prospective multicenter observational study utilizing the KORHN-PRO registry (Kim YJ et al.) revealed that the optimal neuroprognostication thresholds for NSE differ significantly depending on the initial CA rhythm [18].

The underlying rationale is deeply rooted in the pathophysiology of the arrest. Patients presenting with shockable rhythms (e.g., ventricular fibrillation or pulseless ventricular tachycardia) typically experience primary cardiac events. In contrast, non-shockable rhythms (e.g., asystole or pulseless electrical activity) often result from progressive hypoxia or asphyxia, generally involving longer periods of no-flow and low-flow before ROSC is achieved [18]. This disparity results in fundamentally different burdens of hypoxic-ischemic encephalopathy. These two distinct patient populations exhibit entirely different biomarker release kinetics and peak concentrations [18].

Therefore, applying a single, universal NSE cutoff value across all comatose CA survivors significantly reduces predictive accuracy. To maintain a strict FPR of <1% and avoid the tragic premature withdrawal of care in patients who might otherwise recover, clinicians must individualize prognostic algorithms. NSE thresholds must be explicitly stratified and interpreted based on the specific initial mechanism of the patient's CA [16, 18].

4.4. NSE as a Predictor of Favorable Outcomes

Historically, the clinical application of serum biomarkers in post-cardiac arrest care was almost exclusively restricted to predicting futility. Traditional algorithms and international guidelines primarily utilized high concentrations of NSE to identify patients with an unequivocally poor prognosis, thereby supporting decisions to WLST [15, 16]. However, recent evidence has significantly expanded the utility of these biochemical markers, shifting the clinical paradigm toward actively predicting neurological recovery.

A pivotal study by Kim D et al. investigated the prognostic value of maintaining "normal" physiological levels of NSE in comatose survivors. They established that consistently

low, normal NSE values (remaining within the standard laboratory reference range, typically ≤ 16.3 to 17 ng/mL depending on the specific assay) measured at 24, 48, and 72 hours post-arrest, serve as an independent, robust predictor of a highly favorable neurological outcome and successful awakening (e.g., reaching a Cerebral Performance Category of 1 or 2) [30].

This kinetic trajectory—characterized by the distinct absence of a delayed ischemic biomarker surge—indicates that the secondary reperfusion injury was successfully mitigated or minimal [30]. For intensive care clinicians, this conceptual shift is critical. Rather than merely ruling out death, objective biochemical reassurance allows medical teams to confidently persist with aggressive, prolonged intensive care, mechanical ventilation, and targeted temperature management for comatose patients demonstrating these consistently low NSE trajectories. Therefore, integrating normal NSE values into multimodal assessment actively protects patients with a high potential for meaningful functional recovery from premature prognostic pessimism and inappropriate WLST [16, 30].

5. Discussion

The transition from routine deep therapeutic hypothermia (32°C–34°C) to strict normothermia (≤37°C) reflects a major advancement in post-resuscitation science [14, 15]. While recent systematic reviews and the comprehensive Cochrane analysis provide high-certainty evidence that routine deep cooling does not yield superior global outcomes for broad, undifferentiated populations, a critical paradox remains: the pathophysiological rationale for neuroprotection via cooling remains undeniably robust in preclinical animal models [9, 10, 20]. As Skrifvars and Abella argue, the lack of clinical benefit in recent mega-trials may stem largely from their heterogeneous "all-comer" patient populations. This suggests that specific clinical subgroups—characterized by distinct ischemic burdens or initial rhythms—might still fundamentally require and benefit from lower target temperatures, an effect currently masked in massive, generalized trial data [13].

A critical clinical implication of this paradigm shift is the absolute necessity of avoiding therapeutic nihilism. Normothermia is not a passive, hands-off strategy; rather, it is the rigorous, active control of core temperature to aggressively prevent rebound pyrexia and secondary inflammatory surges [3, 14]. Achieving this operational standard is highly resource-intensive. It demands the continuous use of advanced, highly precise cooling devices—with recent data suggesting intravascular systems provide superior thermal stability—alongside formalized, multi-tiered pharmacological protocols to definitively suppress the detrimental shivering reflex [25, 28].

In addition, the implementation of multimodal neuroprognostication requires extreme clinical caution. The shift away from universal guidelines toward relying on nuanced biomarker kinetics—such as utilizing individualized NSE thresholds based explicitly on whether the initial arrest rhythm was shockable or non-shockable—marks a critical evolution [18]. When combined with the rigorous avoidance of premature assessment (mandated by the latest NCS guidelines) and the careful monitoring of laboratory confounders like hemolysis, this approach epitomizes the move toward precision medicine [16, 19].

In conclusion, the scientific community is actively abandoning the historical "one-size-fits-all" approach. The future of post-cardiac arrest intensive care lies in highly personalized management: defining optimal temperature targets and durations for specific patient phenotypes, while concurrently exploring novel, ultra-early therapeutic interventions—such as ultrafast intra-arrest cooling and the pharmacological modulation of the gut-brain neuroinflammatory axis—to comprehensively conquer PCAS [7, 24].

6. Conclusions

The clinical management of comatose survivors following CA has undergone a fundamental paradigm shift, moving away from universal cooling protocols toward highly individualized, precision-based intensive care. Current high-certainty evidence, consolidated by international consensus and the latest systematic reviews, no longer supports the routine application of deep therapeutic hypothermia (32°C–34°C) for the general OHCA population [14, 15].

Instead, the modern standard of care mandates a strategy of rigorous, active normothermia, ensuring that the core body temperature is strictly maintained at $\leq$37°C. Clinicians should recognize that normothermia is not a passive observation but an active intervention. Achieving this goal requires the immediate initiation of care—ideally starting in the Emergency Department—and the continuous use of automated TFS [4, 17]. IC systems are preferred for their superior thermal stability and ability to minimize detrimental temperature fluctuations [25]. Successful temperature control is inseparable from standardized pharmacological protocols designed to aggressively suppress the shivering reflex, which otherwise destabilizes hemodynamics and exacerbates secondary brain injury [11, 15].

Neurological prognostication must also be approached with renewed caution and precision. To prevent the critical risk of a false pessimistic prognosis, multimodal assessments must be strictly delayed until at least 72 hours post-ROSC, following the clearance of all sedative confounders [14, 16]. The interpretation of biochemical markers, specifically NSE,

marks a critical evolution toward personalized medicine. Rather than applying a single universal threshold, clinicians must individualize NSE cutoffs based on the initial CA rhythm (shockable vs. non-shockable) and maintain a zero-tolerance policy for laboratory confounders such as sample hemolysis, which can lead to the inappropriate WLST [18, 19].

In summary, the future of post-resuscitation care lies in moving beyond "one-size-fits-all" targets. By tailoring temperature management and prognostic strategies to specific patient phenotypes, and by exploring emerging frontiers such as the gut-brain neuroinflammatory axis and ultrafast intra-arrest cooling, the medical community is poised to significantly improve the neurological recovery and long-term survival of CA victims [7, 15].

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Funding statement: The study did not receive special funding.

Institutional review board statement: Not applicable.

Informed consent statement: Not applicable.

Data availability statement: Not applicable.

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

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