RJNMSR
Review Journal of Neurological & Medical Sciences Review

Volume 3, Issue 2, 2025

PREDICTIVE VALUE OF HYPERTHERMIA ON NEUROLOGICAL OUTCOMES IN SEVERE TRAUMATIC BRAIN INJURY

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DOI: https://doi.org/10.5281/zenodo.17838769

Received	Accepted	Published
07 April 2025	05 June 2025	15 June 2025

ABSTRACT

Background:

Hyperthermia is a frequently observed physiological disturbance after traumatic brain injury (TBI) and has been linked to secondary brain insults that worsen neurological outcomes. Post-traumatic hyperthermia may result from hypothalamic dysfunction due to direct injury, cerebral inflammation, metabolic derangements, or early infectious processes. Despite extensive global research, local data regarding early hyperthermia as a prognostic indicator in severe TBI remains scarce in Pakistan.

Objective:

To determine the predictive value of early hyperthermia on mortality and neurological outcomes in patients presenting with moderate to severe traumatic brain injury at JPMC, Karachi.

Methods:

A prospective observational study was conducted at JPMC over six months. One hundred patients aged 13 years and above, presenting within four hours of acute head trauma with documented fever within three days, were enrolled. Patients with polytrauma, congenital CNS anomalies, vascular lesions, tumors, or spinal injuries were excluded. Temperature measurements, Glasgow Coma Scale (GCS), radiological findings, and neurological assessments were recorded. Outcomes were assessed using the Glasgow Outcome Scale (GOS) at three months. Data were analyzed using SPSS v22.

Results:

Early hyperthermia (≥38°C within the first 72 hours) was recorded in 48% of patients. Mortality at three months was significantly higher in hyperthermic patients (43.7%) compared to normothermic patients (21.1%). Poor neurological outcome (GOS 1–3) occurred in 68.7% of the hyperthermia group versus 39.4% of the normothermia group. Multivariate logistic regression demonstrated that hyperthermia was an independent predictor of poor outcome (OR 2.81, p = 0.008) after adjusting for age, initial GCS, and CT findings.

Conclusion:

Hyperthermia within the early post-injury period is a strong and independent predictor of poor neurological outcomes and increased mortality in severe TBI patients. Early targeted temperature management and aggressive fever control should be considered integral components of acute neurocritical care protocols to improve outcomes in this population.

Keywords: *Traumatic brain injury, Hyperthermia, Glasgow Outcome Scale, Prognostic factors, Neurocritical care, Mortality*

INTRODUCTION

1.1 Background

Traumatic brain injury (TBI) remains a leading cause of mortality and long-term disability worldwide, with recent global estimates indicating that more than 69 million individuals sustain TBI each year. The burdens of morbidity and loss of productivity fall disproportionately on low- and middle-income countries, where road traffic collisions, limited pre-hospital care, and resource constraints contribute to high case volumes. After the primary mechanical insult, a cascade of secondary injury mechanisms unfolds, including cerebral edema, excitotoxicity, inflammation, oxidative stress, and mitochondrial dysfunction. Elevated core body temperature during the early phase following TBI constitutes a modifiable secondary insult that amplifies metabolic demand, impairs cellular energetics, disrupts the blood–brain barrier, and increases neuronal apoptosis; collectively, these processes worsen clinical outcomes and increase mortality risk [1–4]. Hyperthermia in the acute post-injury period may result from direct hypothalamic injury, systemic inflammatory responses, or early infectious complications, and distinguishing neurogenic fever from infectious fever is often difficult in the intensive care setting. Evidence from large datasets and critical reviews indicates that fever of any etiology in the first 72 hours correlates with poorer neurological recovery, higher intracranial pressure (ICP) burden, and greater need for advanced critical care interventions [2–4]. Despite these data, implementation of structured temperature monitoring and targeted temperature management (TTM) protocols is inconsistent in many low-resource settings, creating an urgent need for locally generated evidence to inform practice.

1.2 Rationale of the Study

Regional data on the frequency and prognostic significance of early hyperthermia after TBI are sparse. Understanding whether fever within the first 72 hours predicts mortality and functional outcome in the local patient population will inform triage, monitoring, and therapeutic priorities. Early hyperthermia offers a readily measurable parameter that could serve as an early warning sign for secondary brain injury and guide implementation of low-cost fever-control strategies in resource-constrained neurocritical care environments. Establishing the magnitude and direction of the association between early hyperthermia and three-month neurological outcome will support the development of targeted ICU protocols, optimize allocation of limited cooling resources, and strengthen pre-emptive family counseling about prognosis. This study therefore aims to evaluate whether early hyperthermia independently predicts neurological outcomes at three months in patients with moderate to severe TBI admitted to a tertiary care center.

1.3 Aim of the Study

The primary aim of the study is to evaluate the predictive value of early hyperthermia on neurological outcomes at three months in patients with moderate to severe traumatic brain injury.

1.4 Objectives

The primary objective is to determine whether hyperthermia occurring within the first 72 hours after traumatic brain injury predicts neurological outcome measured by the Glasgow Outcome Scale (GOS) at three months. Secondary objectives are to quantify the magnitude and frequency of early hyperthermia in this population, to assess the association between early hyperthermia and three-month mortality, to correlate early temperature measures with GOS scores, and to identify additional clinical variables that influence outcome.

1.5 Operational Definitions

Traumatic Brain Injury (TBI):
Acute brain injury resulting from external mechanical force.

Hyperthermia:
A core body temperature of **≥ 38°C** measured via oral, tympanic, or axillary route within the first **72 hours** post-injury.

Neurological Outcome:
Categorized using **Glasgow Outcome Scale (GOS)** at three months.

Severe TBI:
GCS ≤ 8 on admission.
Moderate TBI:
GCS 9–12 on admission.

LITERATURE REVIEW

2.1 Overview

The pathophysiology of TBI includes both primary mechanical damage and a secondary cascade that offers opportunities for therapeutic intervention. Secondary injury is mediated by ischemia, inflammation, excitotoxicity, oxidative stress, and dysregulated thermoregulation; fever plays an important and modifiable role in this cascade. The evidence base from multiple cohorts and meta-analyses demonstrates that fever within the early post-injury period is common and frequently associated with worse clinical trajectories [2, 4]. Studies across diverse healthcare systems indicate that temperature control is an integral component of neurocritical care bundles intended to reduce secondary injury burden.

2.2 Pathophysiology of Hyperthermia After TBI

Elevations in core temperature after head trauma arise through multiple mechanisms. Direct injury to hypothalamic thermoregulatory centers and neurogenic disruption of autonomic control lead to central fever syndromes characterized by persistent, high-grade fever that is often refractory to standard antipyretics. Exaggerated systemic inflammatory responses with release of cytokines such as IL-1, IL-6 and TNF-α can reset the hypothalamic set point and perpetuate pyrexia. Hyperthermia raises cerebral metabolic rate, destabilizes mitochondrial membranes, potentiates oxidative stress and excitotoxic neuronal injury, and contributes to blood–brain barrier breakdown; each 1°C increase in temperature corresponds to an approximate 5–7% increase in cerebral metabolic rate, a relationship that is pathophysiologically detrimental in the setting of impaired cerebral autoregulation [3,4]. These mechanisms help explain the association between early fever and increased ICP, longer duration of coma, and poorer functional recovery reported in cohort studies and pooled analyses [1–4].

2.3 Etiology of Post-Traumatic Hyperthermia

Early post-traumatic fever can be neurogenic, infectious, or part of a systemic inflammatory response. Central (neurogenic) fever typically presents early, is high and sustained, and does not respond well to antipyretics, whereas infectious fever may be accompanied by leukocytosis, positive cultures, and other systemic signs. Systemic inflammatory responses after TBI may also produce pyrexia without overt infection. Large registry analyses suggest that early fever within 72 hours is frequently neurogenic in origin, although a definitive separation between central and infectious causes often requires diagnostic testing and clinical correlation [2].

2.4 Incidence of Hyperthermia in TBI

Published incidence estimates vary by injury severity and patient mix. Reported ranges include approximately 22–34% in moderate TBI, 40–60% in severe TBI, and higher rates among patients with diffuse axonal injury. Several studies indicate that roughly half of severe TBI patients develop fever within the first 72 hours after injury, highlighting the clinical relevance of systematic temperature surveillance [3,4].

2.5 Hyperthermia as a Predictor of Poor Neurological Outcome

Multiple cohort studies have demonstrated that early hyperthermia is associated with increased mortality and worse functional outcomes on standard scales such as GOS. Mortality differences reported in large observational datasets show substantially higher death rates among patients with early fever compared with normothermic counterparts. Functional outcomes measured at three and six months are worse in febrile patients, with increased rates of severe disability and lower rates of favorable recovery [2,3]. The relationship between peak temperature and outcome has been found to be approximately linear in several analyses, and duration of fever beyond 24 hours confers additional risk.

2.6 Clinical Assessment and Thresholds

Clinical practice commonly adopts 38.0°C as the threshold for defining fever, while some studies use higher thresholds (for example, 38.5°C) or

consider duration above threshold to refine risk stratification. Early and frequent temperature measurements, correlation with infection workup, and consideration of hypothalamic injury on imaging inform clinical interpretation. Targeted temperature management strategies range from antipyretic pharmacotherapy and surface cooling to invasive endovascular cooling when available; the evidence base supports early fever control as broadly beneficial, even as therapeutic hypothermia trials have produced mixed results for routine use in TBI [5].

2.7 Temperature Management in Low-Resource Settings

In low-resource settings, advanced cooling technology may be unavailable and fever control relies on standardized monitoring, prompt antipyretics, surface cooling measures, and clinical judgment. Local studies to define the incidence and impact of early fever are necessary to prioritize feasible interventions and to guide the incorporation of temperature control into institutional bundles of neurocritical care practice [6].

2.8 Summary

Early hyperthermia after TBI is common and pathophysiologically linked to mechanisms that aggravate secondary brain injury. Epidemiological and clinical data support the association between fever and increased mortality as well as poorer functional outcomes. Given variability in resources and protocols across settings, locally generated data are essential to tailor pragmatic temperature-management strategies.

METHODOLOGY

3.1 Study Design

This study was designed as a **prospective observational cohort study** conducted at Jinnah Postgraduate Medical Centre (JPMC), Karachi. All eligible patients presenting with acute traumatic brain injury (TBI) were enrolled and followed from admission until three months post-injury to determine the predictive value of early hyperthermia on neurological outcomes.

3.2 Study Setting

The study was carried out in the **Emergency Department, Neurosurgery Ward, and Neuro-Intensive Care Unit (ICU)** of Jinnah Postgraduate Medical Centre, one of Pakistan's largest tertiary care referral centers for neurotrauma. The center receives a high volume of severe TBI cases due to road traffic accidents, falls, and assaults, making it an ideal environment for studying early physiological predictors of outcome.

3.3 Study Population and Eligibility

Adult patients aged 13 years and above presenting with acute head trauma and admitted for care were screened. Inclusion criteria required presentation within four hours of injury and documentation of body temperature recordings within the first 72 hours. Patients with polytrauma that precluded meaningful neurological assessment, those with pre-existing neurological disease unrelated to trauma, those with chronic febrile illnesses, and those who had sustained spinal cord trauma or prior major cranial neurosurgery were excluded to reduce confounding.

3.4 Sample Size and Sampling

A target sample of 100 patients was selected for feasibility and consistency with similar prospective observational cohorts. Consecutive non-probability sampling was used; all eligible patients admitted during the study period were enrolled to minimize selection bias.

3.5 Data Collection Instruments and Procedures

A structured data collection proforma captured demographic information, mechanism and timing of injury, initial Glasgow Coma Scale (GCS), imaging classification, serial temperature readings (every four hours for the first 72 hours), vital signs, and laboratory markers. Temperature measurements were performed with calibrated digital thermometers using standardized techniques. Neurological assessments were recorded at baseline, 24 hours, 72 hours and at three months, with the Glasgow Outcome Scale (GOS) used to determine the primary endpoint at three months. All data collectors were trained to ensure inter-rater consistency.

3.6 Definitions and Outcome Measures

Early hyperthermia was defined as any measured core temperature of 38.0°C or higher within the first 72 hours. The primary outcome was the three-month neurological status assessed by GOS. Secondary outcomes included in-hospital complications, duration of ICU stay, episodes of raised intracranial pressure requiring intervention, and three-month mortality.

3.7 Statistical Analysis

Data were analyzed using standard statistical software. Continuous variables were assessed for normality with the Anderson–Darling test and summarized as means with standard deviations or medians with interquartile ranges as appropriate. Categorical variables were summarized as counts and percentages. Comparative analyses used independent t-tests for normally distributed continuous variables, with Levene's test for homogeneity of variances, and chi-square tests for categorical comparisons. Correlation analyses employed Pearson's correlation coefficient where assumptions were met. Multivariable logistic regression modeling assessed whether early hyperthermia independently predicted poor neurological outcome (GOS ≤ 3) after adjustment for confounders such as age, admission GCS, and CT classification. Statistical significance was defined as $p < 0.05$.

3.8 Ethical Considerations

The study protocol received institutional review board clearance. Informed consent was obtained from each patient's legal representative when necessary. Confidentiality was maintained through de-identification of data and restricted access by the study team. No additional invasive procedures beyond routine clinical care were performed for research purposes.

RESULTS

A total of **100 patients** with acute traumatic brain injury presenting within four hours of trauma were enrolled in the study. All patients were followed from admission until three months post-injury for outcome assessment using the Glasgow Outcome Scale (GOS). The results are presented below.

4.1 BASELINE CHARACTERISTICS

Table 1 presents the demographic and clinical profile of the study population.

Table 1. Baseline Characteristics of the Study Population (n = 100)

Variable	Mean ± SD / n (%)
Age (years)	32.6 ± 14.3
Gender: Male	72 (72%)
Gender: Female	28 (28%)
Mechanism of Injury – Road Traffic Accident	61 (61%)
Mechanism of Injury – Fall	24 (24%)
Mechanism of Injury – Assault	15 (15%)
GCS on Admission (mean)	8.9 ± 3.4
Severe TBI (GCS ≤ 8)	47 (47%)

Moderate TBI (GCS 9–12)	32 (32%)
Mild TBI (GCS 13–15)*	21 (21%)

(Mild TBI included because patients met fever criteria; however, primary analysis focuses on moderate/severe groups.)

4.2 INCIDENCE AND PATTERN OF HYPERTHERMIA

Hyperthermia (≥ 38°C) within the first 72 hours was observed in **48%** of patients.

Table 2. Temperature Characteristics in the First 72 Hours

Variable	**Mean ± SD / n** (%)
Temperature on Admission (°C)	37.4 ± 0.6
Peak Temperature within 72 hours (°C)	38.5 ± 0.7
Patients with Hyperthermia (≥ 38°C)	48 (48%)
Duration of Fever ≥ 24 hours	29 (29%)
Neurogenic Fever (no infection identified)	34 (34%)
Infectious Fever (documented infection)	14 (14%)

4.3 RADIOLOGICAL FINDINGS

Head CT results were classified using the Rotterdam CT Score.

Table 3. Radiological Findings

Variable	**n** (%)
Rotterdam Score 2	18 (18%)
Rotterdam Score 3	29 (29%)
Rotterdam Score 4	33 (33%)
Rotterdam Score 5	20 (20%)
Midline Shift > 5 mm	41 (41%)
Basal Cistern Compression	36 (36%)

Hyperthermia was more common among patients with Rotterdam Score ≥ 4.

4.4 IN-HOSPITAL OUTCOMES

Table 4. In-Hospital Clinical Course

Variable	Hyperthermia Group (n=48)	Normothermia Group (n=52)	p-value
Required intubation	39 (81.3%)	27 (51.9%)	0.003
ICU stay (days, mean ± SD)	9.2 ± 3.1	6.1 ± 2.7	<0.001
Episodes of raised ICP	24 (50%)	11 (21.1%)	0.002
Ventilator-associated pneumonia	10 (20.8%)	4 (7.7%)	0.04

Hyperthermic patients had significantly worse ICU course.

4.5 THREE-MONTH NEUROLOGICAL OUTCOME

Neurological outcome was assessed using the Glasgow Outcome Scale (GOS).

Table 5. Three-Month GOS Outcomes

GOS Category	Hyperthermia Group (%)	Normothermia Group (%)
GOS 1 – Death	21 (43.7%)	11 (21.1%)
GOS 2 – Vegetative	4 (8.3%)	2 (3.8%)
GOS 3 – Severe Disability	8 (16.7%)	8 (15.4%)
GOS 4 – Moderate Disability	10 (20.8%)	18 (34.6%)
GOS 5 – Good Recovery	5 (10.4%)	13 (25.0%)

Interpretation:

Poor outcomes (GOS 1–3) occurred in:

- **68.7**% of hyperthermic patients

39.4% of normothermic patients (p = 0.006)

Hyperthermia strongly correlated with worse neurological recovery.

4.6 CORRELATION BETWEEN PEAK TEMPERATURE AND GOS

A pearson correlation was performed to evaluate the association between peak temperature and gos score.

- **Correlation coefficient (r): –0.42**

p = 0.001

This indicates a moderate negative correlation:

Higher temperature → worse GOS outcome.

4.7 LOGISTIC REGRESSION ANALYSIS

A multivariate logistic regression model was used to identify independent predictors of poor outcome (GOS ≤ 3).

Table 6. Logistic Regression for Predictors of Poor Neurological Outcome

Variable	Odds Ratio (OR)	95% CI	p-value
Hyperthermia (≥ 38°C)	2.81	1.28–6.14	0.008
Initial GCS	0.83	0.73–0.94	0.004
Rotterdam CT Score	1.52	1.15–2.03	0.003
Age	1.01	0.98–1.05	0.40

Interpretation:

After adjusting for confounders, hyperthermia remained an independent predictor of poor neurological outcome.

4.8 SUMMARY OF KEY FINDINGS

1. Early hyperthermia occurred in **48%** of TBI patients.

Hyperthermia was significantly associated with:

- Higher mortality
- Longer ICU stay
- Increased ICP episodes
- Poorer functional outcome

2. Peak temperature strongly correlated with GOS (negative correlation).
3. Hyperthermia independently predicted poor outcome on multivariate analysis.

This establishes hyperthermia as a robust prognostic factor in moderate-to-severe TBI.

DISCUSSION

This prospective observational study evaluated the predictive value of early hyperthermia on neurological outcomes in patients with traumatic brain injury (TBI) presenting to a major tertiary care hospital in Pakistan. The findings demonstrate that hyperthermia within the first 72 hours after injury is strongly associated with higher mortality, poorer Glasgow Outcome Scale (GOS) scores, increased ICU complications, and prolonged hospital stay. These results reinforce existing international evidence and provide critical

local data regarding the prognostic impact of fever in neurotrauma.

5.1 Principal Findings

This prospective cohort study demonstrated that early hyperthermia within the first 72 hours following traumatic brain injury is common and is independently associated with poor neurological outcome at three months. The incidence of fever in the cohort was 48%, and febrile patients experienced higher mortality, longer ICU stay, more episodes of raised intracranial pressure, and a higher frequency of ventilator-associated infection. After adjustment for key clinical confounders, early hyperthermia increased the odds of poor outcome nearly threefold, underlining its role as a significant prognostic marker.

5.2 Comparison with Existing Evidence

The observed incidence and outcome associations are consistent with international cohorts and registry analyses that report similar frequencies of early fever and link hyperthermia to increased mortality and disability [2–4]. The moderate negative correlation between peak temperature and GOS aligns with prior findings that higher peak temperatures and longer durations of fever confer greater risk [2]. The persistence of hyperthermia as an independent predictor in multivariable models supports the view that temperature abnormalities contribute pathophysiologically to secondary brain injury rather than merely serving as markers of initial insult severity.

5.3 Pathophysiological Interpretation

The association between fever and adverse neurological outcome is biologically plausible. Elevations in temperature increase cerebral metabolic rate and oxygen consumption, which in the presence of impaired cerebral perfusion and autoregulation can lead to relative ischemia, worsening edema, and propagation of neuronal injury. Fever-driven inflammatory cascades and blood–brain barrier disruption further amplify secondary injury pathways. These mechanisms collectively explain the observed clinical trajectory of febrile patients, namely increased ICP episodes and prolonged critical care needs [3,4].

5.4 Clinical Implications

From a clinical standpoint, early and frequent monitoring of temperature should be emphasized in TBI protocols, with clear thresholds and escalation pathways for fever control. Even in resource-limited environments where advanced cooling devices may be unavailable, low-technology interventions such as scheduled antipyretics, surface cooling, and vigilant infection surveillance may mitigate the deleterious effects of fever. The data support incorporating temperature parameters into prognostic models used for triage and family counseling.

5.5 Strengths and Contextual Relevance

The prospective design with serial temperature measurements and standardized three-month outcome assessment strengthens causal inference and supports local applicability. The study addresses a regional gap in evidence and provides an empirically derived rationale for prioritizing fever management in neurocritical care pathways.

CONCLUSION

This prospective study demonstrated that early hyperthermia within the first 72 hours following traumatic brain injury is a significant and independent predictor of poor neurological outcomes and increased mortality. Nearly half of all patients presenting with acute TBI developed fever during the early post-injury period, highlighting its high incidence and clinical relevance in neurotrauma care.

Patients who experienced hyperthermia showed substantially worse in-hospital trajectories, including increased frequency of intracranial pressure crises, longer ICU stays, and a higher incidence of secondary complications such as ventilator-associated pneumonia. Importantly, hyperthermia was strongly associated with poorer functional outcomes at three months, and logistic regression confirmed that fever served as an independent prognostic marker even after adjusting for confounders such as initial GCS and CT severity scores.

These findings affirm observations from international literature that hyperthermia

contributes significantly to secondary brain injury by increasing metabolic demand, exacerbating inflammation, and worsening cerebral edema. In the context of Pakistan, where tertiary care centers routinely encounter high volumes of neurotrauma, early identification and aggressive management of hyperthermia are essential components of care. This study provides valuable local evidence supporting the inclusion of structured temperature monitoring and management protocols in TBI treatment guidelines.

Overall, the results highlight hyperthermia as a clinically important, measurable, and modifiable physiological parameter that should be prioritized in acute TBI care to improve neurological recovery and survival.

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