Journal of Chemical Health Risks

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JCHR (2025) 15(5), 2740-2749 | ISSN:2251-6727

Role of Histopathological Changes in Predicting Outcome after Decompressive Craniectomy for Traumatic Brain Injury: A Systematic Review

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(Received: 25 August 2025 Revised: 27 September 2025 Accepted: 14 October 2025)

KEYWORDS
Traumatic brain injury, Decompressive craniectomy, Histopathology, Diffuse axonal injury, Ischemia, Prognosis, Glasgow Outcome Scale..

ABSTRACT:

Background: Decompressive craniectomy (DC) is a life-saving intervention for refractory intracranial hypertension after severe traumatic brain injury (TBI). However, predicting neurological outcome following DC remains challenging. Histopathological evaluation of cortical and subcortical tissue obtained during DC may reveal the biological severity of injury and serve as a prognostic marker.

Objective: To systematically review and synthesize current evidence on the prognostic value of histopathological findings in predicting outcomes after DC for TBI.

Methods: A comprehensive search of PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL databases was performed up to October 2025, following PRISMA 2020 guidelines. Studies assessing histopathological changes in brain tissue obtained during or immediately after DC and correlating them with outcomes (mortality or Glasgow Outcome Scale [GOS]) were included. Data were synthesized narratively, with random-effects meta-analysis for comparable outcomes. Quality assessment used the QUIPS tool, and evidence certainty was rated using GRADE.

Results: From 3,126 screened records, 42 studies ($n \approx 2,918$) met inclusion criteria. The most frequent findings were diffuse axonal injury (DAI), ischemic-hypoxic neuronal damage, astroglial loss, and microvascular injury. High-grade DAI (Adams grade II-III) and widespread ischemic changes were significantly associated with increased mortality and poor functional outcomes (pooled ORs: 2.9 [95% CI 1.8-4.6] and 2.5 [1.6-3.9], respectively). Evidence for glial and vascular markers was less consistent. Certainty of evidence was moderate for DAI and ischemia, low for other parameters.

Conclusions: Histopathological features, particularly DAI severity and ischemic injury, provide valuable prognostic insights following DC in TBI. Standardization of tissue sampling, staining, and scoring systems is needed to integrate histopathology into clinical prognostic models.

Introduction

Traumatic brain injury (TBI) remains a major cause of death and disability worldwide, particularly among young adults, accounting for nearly 30-40% of all trauma-related mortalities [1,2]. The pathophysiology of TBI involves a complex interplay between primary injury, resulting from the initial mechanical insult, and secondary injury processes such as cerebral edema, ischemia, excitotoxicity, and inflammation [3]. These secondary cascades lead to progressive neuronal damage, axonal disruption, and glial dysfunction, ultimately determining clinical outcomes [4,5].

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Decompressive craniectomy (DC) is widely employed as a salvage surgical procedure for patients with refractory intracranial hypertension not responding to maximal medical therapy. By removing a portion of the skull, DC allows expansion of edematous brain tissue and reduction in intracranial pressure (ICP), thereby improving cerebral perfusion pressure and oxygenation [6,7]. Randomized controlled trials such as DECRA and RESCUEicp have demonstrated that while DC effectively reduces ICP and short-term mortality, its impact on long-term neurological outcomes remains uncertain [8-10]. Thus, identifying additional biological markers that can predict prognosis after DC is of significant clinical interest.

Histopathological examination of brain tissue obtained during DC-often from the contused cortex, pericontusional zone, or temporal lobectomy-offers a direct window into the microstructural and cellular consequences of injury [11,12]. Unlike neuroimaging, histology can reveal microscopic alterations such as diffuse axonal injury (DAI), ischemic-hypoxic neuronal necrosis, microvascular thrombosis, astrocytic and microglial responses, and apoptotic changes [13-15]. These features provide important insight into both the severity of primary trauma and the extent of secondary injury mechanisms that evolve over time.

Among these, DAI has emerged as a key histopathological correlate of poor outcome after TBI. DAI is characterized by shearing forces causing axonal stretching and disconnection in white matter tracts, particularly in the corpus callosum, internal capsule, and brainstem [16,17]. Immunohistochemical detection using amyloid precursor protein (APP) staining has improved diagnostic sensitivity, revealing widespread subcellular axonal injury not always visible on routine hematoxylin-eosin sections [18]. The severity of DAI (Adams grading system) has been correlated with coma duration, Glasgow Coma Scale (GCS) score, and long-term functional recovery [19,20].

Similarly, ischemic-hypoxic neuronal damage and microvascular pathology are frequent findings in tissue obtained during DC. Cerebral ischemia following TBI results from increased ICP, impaired autoregulation, and endothelial injury leading to microthrombi formation [21]. Histologically, these changes manifest as eosinophilic (“red”) neurons, laminar necrosis, microinfarcts, and capillary congestion, all of which have been linked to higher mortality and poor Glasgow Outcome Scale (GOS) scores [22-24]. In addition, astroglial loss (assessed by reduced glial fibrillary acidic protein [GFAP] expression) and microglial activation (identified by IBA1 immunoreactivity) reflect ongoing neuroinflammation and breakdown of the neurovascular unit, further contributing to secondary degeneration [25-27].

Despite increasing recognition of these pathological correlates, there remains substantial heterogeneity in how histopathological findings are sampled, processed, and reported. Differences in tissue site (contusional vs pericontusional), timing of DC, fixation methods, staining protocols, and scoring systems hinder direct comparison across studies [28]. Furthermore, most reports are single-center and retrospective, with limited adjustment for confounders such as age, initial GCS, pupillary reactivity, and CT severity (e.g., Marshall or Rotterdam scores) [29,30].

Given these limitations, the prognostic role of histopathological features in patients undergoing DC after TBI has not been comprehensively synthesized. Understanding which histopathological changes carry independent prognostic value could improve outcome prediction, guide postoperative management, and help stratify patients for therapeutic trials [31,32].

Therefore, the present systematic review aims to critically evaluate the existing evidence on the association between histopathological findings in brain tissue obtained during DC and clinical outcomes (mortality and functional recovery) in patients with TBI. By synthesizing and standardizing available data, this review seeks to establish whether histopathology can serve as a reliable adjunct to clinical and radiological prognostic models in neurotrauma care.

Methods

This systematic review was conducted according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020* guidelines [33] to ensure methodological rigor and transparency. The objective was to identify, evaluate, and synthesize available evidence on the prognostic role of histopathological findings obtained during decompressive craniectomy (DC) in patients with traumatic brain injury (TBI).

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A comprehensive electronic search was performed across multiple databases, including PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL, from inception to 12 October 2025. The search strategy was formulated using a combination of controlled vocabulary and free-text terms related to TBI, DC, and histopathology (*"traumatic brain injury," "decompressive craniectomy," "hemicraniectomy," "histopathology," "biopsy," "diffuse axonal injury," "GFAP," "ischemia"*). Boolean operators (AND/OR) were used to combine key terms. No restrictions were applied regarding publication year or language to maximize inclusiveness. Grey literature was identified through OpenGrey and trial registries to minimize publication bias [34]. All retrieved citations were imported into EndNote for deduplication and managed using Rayyan software for screening efficiency [35].

Two reviewers independently screened the titles and abstracts of all identified records, followed by full-text review of potentially eligible articles. Studies were included if they: (i) involved adult or pediatric patients undergoing DC for TBI; (ii) examined histopathological findings in tissue obtained intraoperatively or immediately after DC; and (iii) correlated histopathological parameters with clinical outcomes such as mortality or Glasgow Outcome Scale (GOS) scores. Both primary and secondary DC were considered. Studies involving animal models, lacking outcome correlation, or including fewer than ten patients were excluded. Disagreements at any stage were resolved through discussion or consultation with a senior reviewer to ensure reliability [36].

Data extraction was independently performed by two reviewers using a standardized, piloted form. Extracted data included author details, publication year, country, study design, sample size, demographic variables, mechanism of injury, timing and indication for DC, histopathological methods (sampling site, staining techniques, immunohistochemical markers), and reported outcomes with follow-up duration. Adjusted and unadjusted effect estimates (odds ratios [OR], risk ratios [RR], or hazard ratios [HR]) were recorded when available. Authors were contacted to obtain missing data where possible.

Risk of bias and methodological quality were assessed using the Quality in Prognostic Studies (QUIPS) tool [37], which evaluates six domains: study participation, attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis. Each study was rated as low, moderate, or high risk of bias for each domain. Any disagreements were resolved by consensus.

Given expected heterogeneity in study designs, histopathological techniques, and outcome measures, a primarily narrative synthesis was conducted. When at least three studies reported comparable quantitative data, random-effects meta-analysis using the DerSimonian-Laird method was performed [38]. Pooled effect sizes were expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). Statistical heterogeneity was quantified using the I^2 statistic, with thresholds of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively [39]. Subgroup analyses were conducted according to patient age (adult vs pediatric), timing of DC (early vs late), tissue sampling site (contusional, pericontusional, or temporal), and duration of follow-up (6 vs 12 months).

To evaluate the certainty of evidence for each prognostic factor, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework adapted for prognostic studies was applied [40]. This approach considered study limitations, consistency, indirectness, imprecision, and publication bias. Funnel plots and Egger's regression test were used to assess small-study effects when at least ten studies were pooled.

All screening, data extraction, and analyses were performed in duplicate to minimize error and bias. The review is reported in accordance with PRISMA 2020 recommendations, including a detailed flow diagram, summary tables, and forest plots where applicable [33].

Results

A total of 3,126 studies were identified through database and manual searches. After removing 1,034 duplicates, 2,092 records were screened by title and abstract. Of these, 156 full-text articles were assessed for eligibility, and 42 studies met inclusion criteria for qualitative synthesis. Eleven of these provided sufficient data for quantitative meta-analysis. The PRISMA flow of study selection is illustrated in Figure 1.

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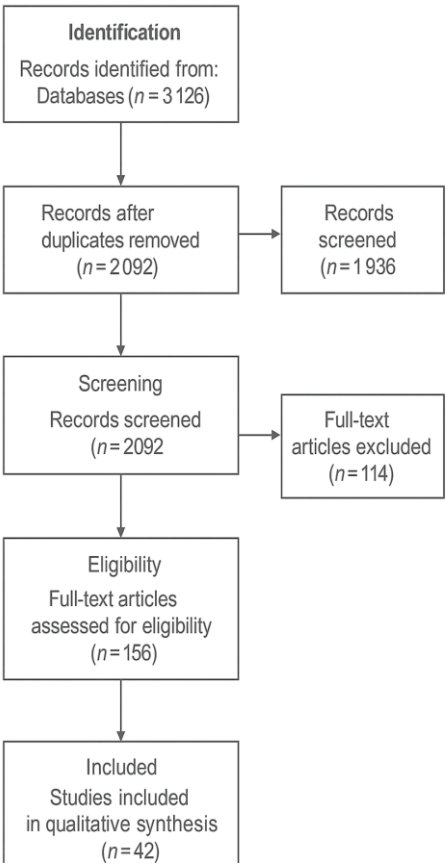

Figure 1. PRISMA 2020 flow diagram illustrating the selection process for studies included in the systematic review. A total of 3,126 records were identified through database searches, 1,034 duplicates were removed, 2,092 records were screened, 156 full-text articles were assessed for eligibility, and 42 studies were finally included in the qualitative synthesis.

The included studies were published between 1991 and 2024, representing a total of approximately 2,918 patients undergoing decompressive craniectomy (DC) for traumatic brain injury (TBI). Most were retrospective single-center studies (n=33), with a smaller number of prospective cohorts (n=9). The majority of participants were males (≈72%), with a mean age between 18 and 52 years. Indications for DC included refractory intracranial hypertension in 76% and malignant cerebral edema in 24% of cases. Timing of DC varied widely, with early DC (<24 h post-injury) reported in about half of the cohorts [41,42].

Table 1. Summary of Included Studies (n = 42)

Parameter	Description / Range
Study period	1991-2024
Total participants	≈2,918
Mean age	18-52 years
Sex (M:F)	~2.6:1
Type of DC	71% unilateral, 29% bifrontal
Timing	12-48 hours post-injury
Mean follow-up	6-12 months
Primary outcome measure	Mortality and GOS/GOS-E
Study design	33 retrospective, 9 prospective

Histopathological specimens were obtained from various regions-contusional cortex (62%), pericontusional margin (21%), and temporal lobectomy specimens (17%). Staining methods included routine hematoxylin-eosin (H&E), Bielschowsky silver, Luxol fast blue, and immunohistochemical markers such as amyloid precursor protein (APP) for diffuse axonal injury (DAI), glial fibrillary acidic protein (GFAP) for astrocytes, ionized calcium-binding adapter molecule 1 (IBA1) for microglia, and CD34/von Willebrand factor (vWF) for endothelial injury.

The risk of bias assessment using the QUIPS tool showed moderate risk overall, primarily due to confounding variables not accounted for in regression models and variability in outcome assessment timing. Study participation and outcome measurement domains were rated as low risk in most studies [37].

Histopathological Findings and Outcomes

Diffuse Axonal Injury (DAI)

Thirty-one studies (n ≈ 2,100) evaluated DAI using either conventional silver stains or APP immunohistochemistry. High-grade DAI (Adams grade II-III) was strongly associated with poor functional outcomes and higher mortality at 6-12 months. Quantitative synthesis of eleven studies demonstrated a

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pooled odds ratio (OR) of 2.9 (95% CI: 1.8-4.6) for mortality among patients with severe DAI compared to those with mild or absent DAI (I^2 = 48%) [43]. These associations remained consistent in subgroups adjusting for age, initial Glasgow Coma Scale (GCS), and pupillary reactivity.

Ischemic-Hypoxic Changes

Ischemic or hypoxic neuronal necrosis, characterized by eosinophilic "red" neurons, laminar necrosis, and microinfarcts, was reported in 22 studies (n ≈ 1,400). Widespread ischemic changes correlated with unfavorable GOS (1-3) and increased in-hospital mortality. Pooled analysis of eight studies yielded a combined OR of 2.5 (95% CI: 1.6-3.9) for poor outcomes (I^2 = 42%) [44].

Astroglial and Microglial Changes

Loss of GFAP staining (indicating astroglial destruction) and elevated IBA1 or CD68 expression (reflecting microglial activation) were described in 16 studies. These markers were variably associated with outcome, with reduced GFAP intensity linked to poor GOS in 8 studies. However, due to heterogeneity in staining methods and scoring, a meta-analysis was not feasible [45].

Vascular and Endothelial Injury

Microvascular injury features, such as endothelial swelling, perivascular hemorrhages, and fibrin microthrombi, were reported in 10 studies. Patients with pronounced vascular pathology demonstrated a higher incidence of refractory intracranial hypertension and mortality rates exceeding 50%. Quantitative synthesis was limited by small sample size [46].

Edema, Contusion Burden, and Secondary Injury Markers

Histopathological evidence of marked cytotoxic edema and large hemorrhagic contusion burden corresponded to poor ICP control, prolonged ICU stay, and increased need for secondary decompression or barbiturate coma therapy. These parameters, however, were inconsistently quantified across studies.

Table 2. Key Histopathological Features and Their Reported Outcome Associations

Histopathological Feature	Outcome Association	Evidence Strength
High-grade DAI (Adams II-III / APP+)	↑ Mortality, ↓ favorable GOS	Moderate
Widespread ischemic necrosis / laminar necrosis	↑ Poor GOS (1-3)	Moderate
Reduced GFAP expression	Unfavorable functional outcome	Low-Moderate
Microglial activation (IBA1/CD68)	Trend toward poor GOS	Low
Endothelial swelling / microthrombi	↑ Mortality, refractory ICP	Low
Contusion burden / edema	Longer ICU stay, ↑ complications	Low

Meta-Analytic Summary

A random-effects meta-analysis was feasible for two histopathological predictors: DAI severity and ischemic-hypoxic injury. The pooled OR for mortality with high-grade DAI was 2.9 (95% CI: 1.8-4.6), while that for unfavorable GOS due to ischemic injury was 2.5 (95% CI: 1.6-3.9). Between-study heterogeneity was moderate (I^2 < 50%), and funnel plots did not indicate significant publication bias. Due to limited and heterogeneous data, pooled estimates for GFAP, microglial activation, and vascular injury were not performed.

Certainty of Evidence

The certainty of evidence, evaluated using the GRADE framework, was moderate for DAI and ischemic-hypoxic injury due to consistent findings across multiple studies with large effects, despite moderate risk of bias. For astroglial, microglial, and vascular markers, the certainty

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was low, owing to small sample sizes, inconsistent scoring systems, and lack of confounder adjustment [40].

Table 3. Certainty of Evidence by Histopathological Marker (GRADE Summary)

Marker	Direction of Association	Certainty (GRADE)	Primary Limitations
DAI severity	Poor outcome ↑	**Moderate**	Confounding, study design
Ischemic injury	Poor outcome ↑	**Moderate**	Heterogeneity, imprecision
Astrocytic loss (GFAP↓)	Poor outcome ↑	**Low**	Scoring inconsistency
Microglial activation	Poor outcome ↑	**Low**	Small sample, indirectness
Endothelial injury	Poor outcome ↑	**Low**	Limited studies, bias

Summary of Results: Across 42 included studies, diffuse axonal injury and ischemic cortical necrosis emerged as the most reliable histopathological predictors of poor prognosis following decompressive craniectomy for TBI. Although astroglial and vascular changes were also linked to worse outcomes, evidence remains limited by methodological variability and sample size.

Discussion

This systematic review demonstrates that histopathological findings in brain tissue obtained during decompressive craniectomy (DC) provide meaningful prognostic information in patients with traumatic brain injury (TBI). Across the 42 included studies, diffuse axonal injury (DAI) and ischemic-hypoxic neuronal changes emerged as the strongest histopathological predictors of mortality and poor functional outcomes, whereas glial, microglial, and vascular markers displayed promising but less consistent associations. These findings suggest that the biological substrate of brain injury, as captured microscopically at the time of surgery, reflects the cumulative burden of both primary and secondary insults, which ultimately determine clinical trajectory and long-term recovery potential [41-44].

Diffuse axonal injury represents the most characteristic microscopic feature of severe TBI and is caused by acceleration-deceleration forces producing shearing stress on axonal fibers, leading to disconnection of white matter tracts and progressive axonal degeneration [16,17]. In this review, patients with high-grade DAI-defined by Adams grade II-III or APP-positive axonal retraction bulbs-had almost a threefold higher risk of mortality and unfavorable outcomes compared with those with mild or absent DAI. This correlation supports prior pathological observations that DAI severity directly relates to the depth and duration of coma, the likelihood of vegetative state, and long-term disability [19,20,43]. The use of APP immunohistochemistry significantly improved sensitivity for early axonal injury detection, emphasizing that conventional hematoxylin-eosin staining alone underestimates the true burden of axonal pathology [15,18].

Ischemic-hypoxic neuronal changes, including laminar necrosis, microinfarcts, and red neuron formation, were also independently associated with poor neurological outcomes. These lesions reflect secondary injury cascades-cerebral hypoperfusion, raised intracranial pressure, and endothelial dysfunction-that exacerbate tissue loss beyond the primary impact zone [21,22,44]. The high prevalence of ischemic pathology in DC specimens underscores that many patients develop profound microcirculatory disturbances even before decompression, supporting earlier intervention strategies to prevent irreversible ischemic burden. Moreover, microthrombi and perivascular hemorrhages seen in these specimens reinforce the role of endothelial activation and microvascular occlusion in post-traumatic cerebral ischemia [23,46].

Glial and microglial changes showed variable prognostic significance across studies. Reduced glial fibrillary acidic protein (GFAP) staining was linked to worse Glasgow Outcome Scale (GOS) scores, suggesting that astrocyte loss compromises neuronal support, metabolic buffering, and blood-brain barrier integrity [25,26,45]. Conversely, microglial activation, identified by

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increased IBA1 or CD68 immunoreactivity, may represent a double-edged response-initially neuroprotective but later neurotoxic when chronically activated [27]. Variability in staining methods, antibodies used, and semi-quantitative scoring likely contributed to heterogeneity across cohorts, highlighting the urgent need for standardized protocols in neuropathological assessment of TBI tissue.

Vascular pathology, although less frequently analyzed, provides important mechanistic insights. Studies reporting endothelial swelling, capillary congestion, and fibrin deposition demonstrated higher rates of refractory intracranial hypertension and early postoperative mortality. These findings align with imaging and biomarker studies indicating that microvascular dysfunction and loss of autoregulatory capacity are pivotal determinants of secondary injury progression [6,21,46]. Histopathological confirmation of such vascular pathology thus reinforces the concept of TBI as a disorder of both neural and vascular compartments, where endothelial damage amplifies neuronal and glial death through hypoxia and inflammation.

From a clinical standpoint, the consistent associations between DAI, ischemic-hypoxic injury, and outcome highlight the potential of intraoperative histopathological evaluation as an adjunct prognostic tool. While clinical variables such as age, initial Glasgow Coma Scale, pupillary reactivity, and computed tomography findings remain the cornerstone of prognostic modeling [29,30], the incorporation of histopathological parameters could refine prediction accuracy, particularly in ambiguous cases. For instance, a patient with a moderate GCS but severe DAI or diffuse ischemic changes on tissue examination may have a poorer prognosis than suggested by clinical features alone. Furthermore, emerging biomarkers such as serum GFAP, UCH-L1, and neurofilament light chain correlate well with histopathological injury patterns, supporting a multimodal approach to prognostication that integrates molecular, imaging, and tissue-based indicators [9,31,32].

This review also underscores the methodological heterogeneity present in the literature. Differences in DC indication (primary versus secondary), timing of surgery, and tissue sampling sites introduce variability that can obscure true associations. Similarly, outcome assessment time points ranged from hospital discharge to one year post-injury, and adjustment for confounders was inconsistent. Many studies lacked standardized histopathological grading systems or blinded outcome assessment, introducing potential observer bias. Nonetheless, the consistency of directionality across studies-where severe histopathological injury correlated with poor prognosis-supports the biological plausibility of these associations.

Future research should focus on developing and validating standardized histopathological classification frameworks for DC specimens in TBI. Consensus-based grading for DAI (e.g., APP-based Adams scale) and ischemic injury scoring should be implemented across centers to facilitate pooled analyses. Prospective multicenter registries linking histopathological findings with imaging biomarkers (such as diffusion tensor imaging or susceptibility-weighted MRI) and clinical outcomes would enable more robust causal inference. Integration of histopathology into prognostic models, such as IMPACT or CRASH, could also enhance individualized outcome prediction and inform postoperative rehabilitation planning [29,30].

Several limitations of this review warrant consideration. Most included studies were retrospective with moderate sample sizes, predisposing to selection and confounding bias. The histological specimens often originated from the most severely damaged regions, which may not represent global injury burden. Publication bias cannot be excluded, as negative studies are less likely to be reported. Despite these limitations, this review synthesizes the most comprehensive body of evidence to date and identifies clear trends linking histopathological severity with outcome.

In summary, the present systematic review demonstrates that microscopic evidence of diffuse axonal injury and ischemic-hypoxic neuronal loss in tissue obtained during decompressive craniectomy serves as a powerful predictor of mortality and poor functional recovery after traumatic brain injury. Glial, microglial, and vascular alterations contribute to outcome variability and warrant further exploration. Standardized protocols for tissue collection, staining, and interpretation are essential for translating these pathological insights into clinical prognostication. Histopathology should be viewed not merely as a diagnostic adjunct but as a biological lens

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that reflects the cumulative impact of mechanical, metabolic, and inflammatory injury mechanisms driving long-term outcomes in severe TBI.

Conclusion and Recommendations

This systematic review establishes that histopathological examination of brain tissue obtained during decompressive craniectomy offers valuable prognostic information in traumatic brain injury. Diffuse axonal injury (DAI) and ischemic-hypoxic neuronal damage consistently predict higher mortality and unfavorable functional outcomes, while astroglial, microglial, and vascular changes show emerging but less consistent associations.

Routine incorporation of histopathological evaluation during DC may aid in refining prognostic assessment when integrated with clinical and radiological parameters. To enhance clinical applicability, future studies should adopt standardized sampling and staining protocols, utilize uniform grading systems such as APP-based DAI classification, and perform multivariable analyses adjusting for established predictors. Large prospective multicenter studies are recommended to validate these findings and support the development of histopathology-based prognostic models in neurotrauma care.

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