



Quantitative CT biomarkers for early outcome prediction in acute traumatic brain injury: a systematic review, meta-analysis, and meta-regression

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Abstract

Acute traumatic brain injury (TBI) remains one of the leading causes of mortality worldwide, as well as long-term neurological deficits. Early and reliable prognostic measurements play an important role in clinical decision-making, triage procedures, and resource management in urgent care settings. Conventional computed tomography (CT)-based scoring systems, including Marshall, Rotterdam, and Helsinki, are widely used in practice; however, they may be limited by subjectivity and inter-observer variability due to their qualitative or semi-quantitative nature. The present study aimed to conduct a systematic review of the prognostic associations between quantitative CT biomarkers and early neurological outcomes, as well as mortality, in patients with acute TBI. A systematic review and meta-analysis were conducted according to PRISMA 2020 guidelines. Electronic databases including PubMed, Scopus, Embase, and Web of Science were searched from inception until March 2025. Eligible studies included observational and interventional research reporting quantitative CT-derived biomarkers, such as lesion volume, midline shift, basal cistern compression, and ventricular ratios, along with clinical outcomes in adult patients with acute TBI. The QUADAS-2 tool and Newcastle–Ottawa Scale were used to assess risk of bias. Random-effects models were applied to estimate pooled odds ratios (ORs), and heterogeneity was explored using subgroup analyses and meta-regression. A total of 36 studies ($n=18,742$ patients) met inclusion criteria, with 29 contributing to quantitative synthesis. Quantitative CT biomarkers were significantly associated with adverse neurological outcomes (pooled OR=2.41, 95% CI=1.98–2.93) and mortality (pooled OR=2.67, 95% CI=2.11–3.38). Lesion volume and midline shift demonstrated the largest pooled effect sizes among examined biomarkers. Meta-regression analyses identified patient age, injury severity, timing of CT imaging, and biomarker type as significant moderators of effect size. CT imaging performed within 24 h of injury was associated with stronger prognostic associations, likely reflecting acute injury burden rather than causation. Findings were consistent in sensitivity analyses, and no substantial publication bias was detected. The available evidence suggests that quantitative CT biomarkers provide clinically relevant prognostic associations with short-term neurological outcomes and mortality following acute TBI. These objective radiologic measures may complement existing CT-based scoring systems and support early risk stratification within emergency radiology practice. Nevertheless, prospective validation studies and standardized measurement protocols are required before broader clinical implementation.

Keywords Traumatic brain injury · Computed tomography · Quantitative imaging biomarkers · Prognosis · Meta-analysis · Emergency radiology

Introduction

Traumatic brain injury (TBI) is a major global health concern and ranks among the leading causes of death and long-term neurological disability across all age groups. Global epidemiological data indicate that acute TBI accounts for a substantial proportion of emergency department visits, hospitalizations, and intensive care unit admissions. The most frequent causes include road traffic accidents, falls, interpersonal violence, and sports-related injuries, with a disproportionate burden reported in low- and middle-income countries due to limited trauma care infrastructure. One of the principal challenges in early outcome assessment following acute TBI lies in the complexity and heterogeneity of primary and secondary injury mechanisms, despite advances in neurocritical care and imaging technologies [1].

Computed tomography (CT) remains the imaging modality of choice in acute TBI because of its widespread availability, rapid acquisition, cost-effectiveness, and sensitivity in detecting life-threatening intracranial abnormalities such as hemorrhage, mass effect, and herniation. Traditional CT-based scoring systems, including the Marshall, Rotterdam, and Helsinki classifications, are widely used for prognostic assessment. Although these systems provide clinically useful information, they are inherently qualitative or semi-quantitative and may be influenced by interobserver variability, categorical thresholds, and limited sensitivity to subtle injury patterns [2]. Consequently, objective, reproducible, and continuous quantitative CT biomarkers are increasingly being explored as measures that may more precisely reflect injury burden and anatomical severity.

Quantitative CT biomarkers encompass a range of imaging-derived parameters, including lesion volume, degree of midline shift, ventricular compression ratios, basal cistern effacement indices, hematoma density, and regional attenuation measurements. Advances in image processing, artificial intelligence, and automated segmentation techniques have enhanced the feasibility of extracting such metrics in acute settings. Emerging evidence suggests that these biomarkers

demonstrate significant prognostic associations with neurological outcomes and mortality beyond conventional visual assessment approaches [3].

Several systematic reviews and meta-analyses have evaluated prognostic factors in TBI, including clinical variables, biochemical markers, genetic polymorphisms, and advanced neuroimaging modalities. For example, prior reviews have examined the prognostic role of MRI findings [4], blood-based biomarkers such as GFAP and S100B [5, 6], genetic polymorphisms including apolipoprotein E4 [7], functional neurobehavioral deficits such as eye movement abnormalities [8], and diffusion tensor imaging in mild TBI [9]. Emerging frameworks have also proposed transdiagnostic MRI markers related to post-traumatic psychopathology [10]. While these studies contribute valuable insights, many focus on non-CT modalities or integrate multiple prognostic domains without isolating the independent contribution of quantitative CT parameters.

Although the body of primary research investigating quantitative CT features in acute TBI continues to expand, a comprehensive synthesis specifically examining CT-derived quantitative biomarkers and their prognostic associations has been lacking. In several prior reviews, qualitative CT classifications have been combined with clinical predictors, and analyses have frequently focused on diagnostic accuracy rather than outcome association [2, 3]. Furthermore, variability in study design, imaging timing, outcome definitions, and statistical methodology has contributed to inconsistent findings across individual studies.

This gap is particularly relevant in emergency radiology, where timely and reliable prognostic assessment is essential. A systematic review and meta-analysis incorporating meta-regression can provide pooled effect estimates, evaluate consistency across subgroups, and identify sources of heterogeneity in reported associations. Such evidence may contribute to the standardization of quantitative CT biomarkers and support their integration alongside existing CT-based scoring systems in the assessment of acute TBI (Fig. 1).

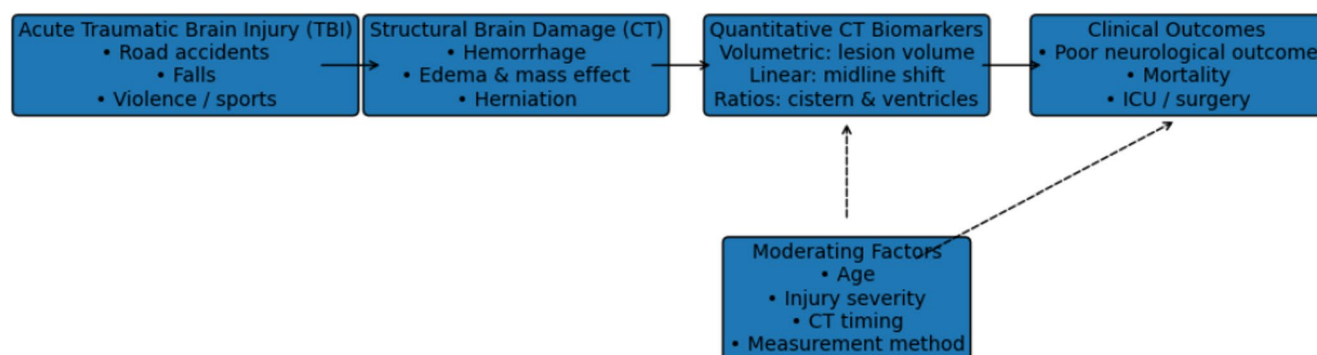


Fig. 1 Conceptual framework illustrating how quantitative CT biomarkers derived from early CT imaging reflect structural injury burden and predict neurological outcome and mortality in acute traumatic brain injury, with moderation by patient and imaging-related factors

Aim and objectives

“The primary goal of the study is to have a systematic review of the prognostic significance of quantitative CT biomarkers in identifying outcomes early among patients with acute traumatic brain injury. This review is aimed at”:

- (i) summarize the existing information on the relationship between the quantitative CT-based indices and the neurological outcome and mortality;
- (ii) identify the synergized effect sizes of prognostic variables using randomly effected meta-analysis;
- (iii) assess the quality of the study and risk of bias; and.
- (iv) explore the sources of heterogeneity using subgroup analysis and meta-regression.

The proposed study will help answer these questions that will allow clarifying the clinical role of quantitative CT biomarkers and their potential to enhance the early risk stratification and decision-making in the treatment of acute TBI.

Methods

Study design and reporting standards

A systematic review, meta-analysis, and meta-regression were conducted based on the regulations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020).

The methodological procedure was uniquely designed to examine prognostic associations between the quantitative computed tomography biomarkers and clinical outcomes in acute traumatic brain injury (TBI) and, therefore, does not address the predictive performances of models.

Literature search strategy

A comprehensive literature search was performed across PubMed (MEDLINE), Scopus, Embase, and Web of Science from database inception to March 2025. The search strategy combined controlled vocabulary (MeSH and Emtree terms) with free-text keywords related to:

- “traumatic brain injury” OR “acute TBI”.
- “Computed tomography” OR “CT”.
- “Quantitative imaging” OR “imaging biomarker”.
- “Lesion volume,” “midline shift,” “cistern compression,” “ventricular ratio”.
- “Prognosis,” “neurological outcome,” “mortality”.

Boolean operators (AND/OR), truncation, and database-specific filters were applied to optimize sensitivity and specificity.

To reduce publication bias, grey literature was searched through Google Scholar, and reference lists of relevant reviews and included studies were manually screened. Only studies published in English were included.

Eligibility criteria (PICOS framework)

Studies were included according to predefined PICOS criteria:

- Population (P): Adults (≥ 18 years) with acute TBI undergoing non-contrast CT within 72 h of injury.
- Index (I): Quantitative CT biomarkers including lesion volume (cm^3), midline shift (mm), basal cistern compression indices (ratio-based), ventricular volume/compression ratios, or other numeric CT-derived measures.
- Comparator (C): Standard CT interpretation, alternative thresholds, or absence of comparator (prognostic association studies were included even without a comparator arm).
- Outcomes (O): Neurological outcome (e.g., Glasgow Outcome Scale or GOS-E) and/or mortality measured at discharge or follow-up (30 days to 12 months).
- Study Design (S): Prospective or retrospective observational studies and randomized controlled trials reporting prognostic associations.

Exclusion criteria included pediatric populations, animal studies, purely qualitative CT analyses, MRI-only or biomarker-only studies, case reports, editorials, and narrative reviews.

Study selection process

All retrieved records were imported into reference management software, and duplicates were removed.

Study selection was performed independently by two reviewers in two stages:

1. Title and abstract screening.
2. Full-text eligibility assessment.

Disagreements were resolved through discussion or adjudication by a third reviewer. Inter-rater agreement was evaluated using Cohen’s kappa statistic.

Data extraction

Data extraction was conducted independently by two reviewers using a standardized and pilot-tested form. Extracted variables included:

- Study characteristics (author, year, country, design, sample size).
- Patient demographics (age, sex distribution).
- Injury characteristics (TBI severity, mechanism, timing of CT).
- Quantitative CT biomarkers (type, unit, measurement method, thresholds, segmentation approach).
- Outcomes (neurological scale, mortality, follow-up timepoint).
- Statistical estimates (odds ratios, adjusted covariates).

Measurement methodology (manual vs. semi-automated vs. automated segmentation) was explicitly recorded to explore methodological heterogeneity.

Risk of bias and quality assessment

The risk of bias was assessed independently by two reviewers.

- QUADAS-2 was applied to studies evaluating imaging-based prognostic performance where CT biomarkers functioned as index tests.
- The Newcastle–Ottawa Scale (NOS) was used for cohort-based observational studies.

Studies were categorized as low, moderate, or high risk of bias based on predefined criteria.

Rationale Although QUIPS is commonly used for prognostic factor reviews, QUADAS-2 was selected due to the diagnostic/prognostic imaging nature of the included studies. This limitation is acknowledged in the discussion.

Statistical analysis

Meta-analysis was conducted using random-effects models (DerSimonian–Laird estimator) to account for clinical and methodological heterogeneity.

Effect estimates were harmonized as odds ratios (ORs) with 95% confidence intervals, reflecting prognostic associations rather than predictive accuracy.

Heterogeneity was evaluated using:

- I^2 statistic (25% low, 50% moderate, 75% high).
- τ^2 (between-study variance).

Sensitivity analyses were performed using restricted maximum likelihood (REML) estimators.

Subgroup and sensitivity analyses

Pre-specified subgroup analyses were conducted based on:

- TBI severity (mild vs. moderate–severe).
- CT timing (<24 h vs. \geq 24 h).
- Biomarker type (volumetric vs. linear vs. ratio-based).
- Measurement technique (manual vs. automated).

Sensitivity analyses included:

- Exclusion of high risk-of-bias studies.
- Leave-one-out influence analysis.

These analyses were used to assess robustness and explore heterogeneity sources.

Meta-regression analysis

Random-effects meta-regression was performed to explore potential moderators of effect size, including:

- Mean patient age.
- Proportion of severe TBI.
- Time from injury to CT acquisition.
- Biomarker category (volumetric vs. other).
- Study design.

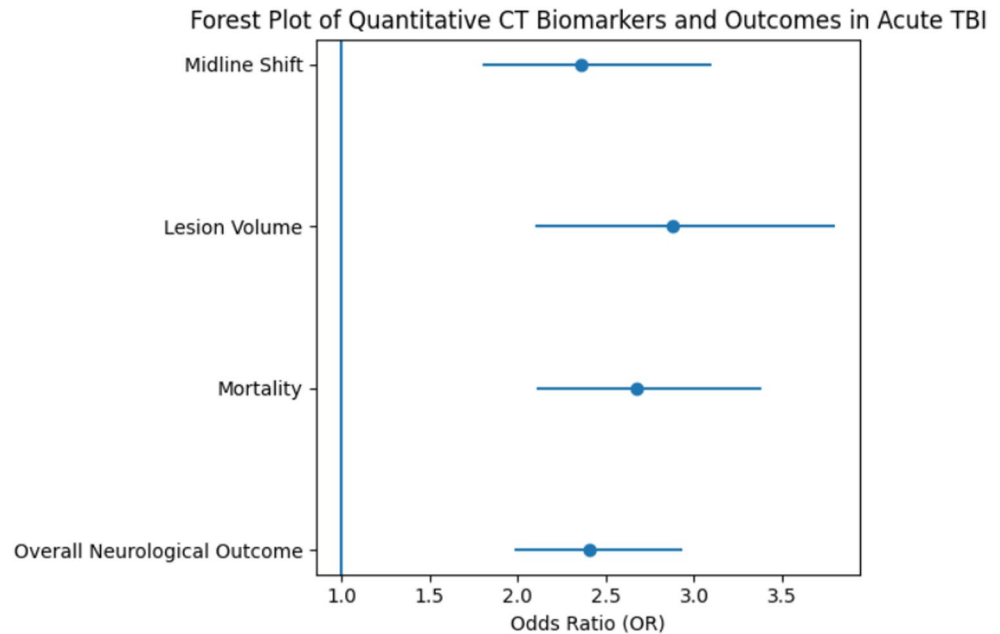
The proportion of between-study variance explained (R^2) was reported (Fig. 2).

Publication bias assessment

Publication bias was evaluated using:

- Funnel plot visual inspection.
- Egger's regression test ($p < 0.10$ indicating small-study effects).
- Trim-and-fill analysis to assess potential impact of missing studies.

Fig. 2 Forest Plot of Quantitative CT Biomarkers and Outcomes in Acute TBI



Outcome harmonization

Given variability in outcome timepoints across studies (discharge, 30-day, 3–12 months), outcomes were categorized as:

- Early outcome (≤ 30 days or discharge).
- Intermediate/long-term outcome (> 30 days).

Primary conclusions focused on early outcome associations, with longer follow-up findings interpreted cautiously (Fig. 3).

Results

Study selection

The search of databases was systematic, and 3,842 records were found in PubMed, Scopus, Embase, and Web of Science. Once the 1,126 duplicate records had been removed, 2716 records were left to be screened. The 2,493 studies were filtered out based on irrelevance, non-TBI groups, no CT imaging, or no quantitative measurement, to form the title and abstract adjudication.

After reviewing 223 full-text articles, 187 of them were filtered by predefined inclusion criteria, including qualitative CT-only studies, MRI or biomarker-only studies, pediatric cohort studies, or inadequacy of outcome data. Thus, 36 papers were included into the qualitative synthesis and 29 were suitable to be included in the quantitative meta-analysis. The PRISMA flow chart is used to show the selection process.

Study characteristics

The list of eligible literature included 18,742 adult patients with acute traumatic brain injury who were published between 2005 and 2025. The types of study designs included retrospective cohort ($n=21$), prospective observational ($n=13$), and randomized trials which included imaging stations ($n=2$). The sample sizes were between 62 and 2716 participants and had a mean age distribution of 34–61 years.

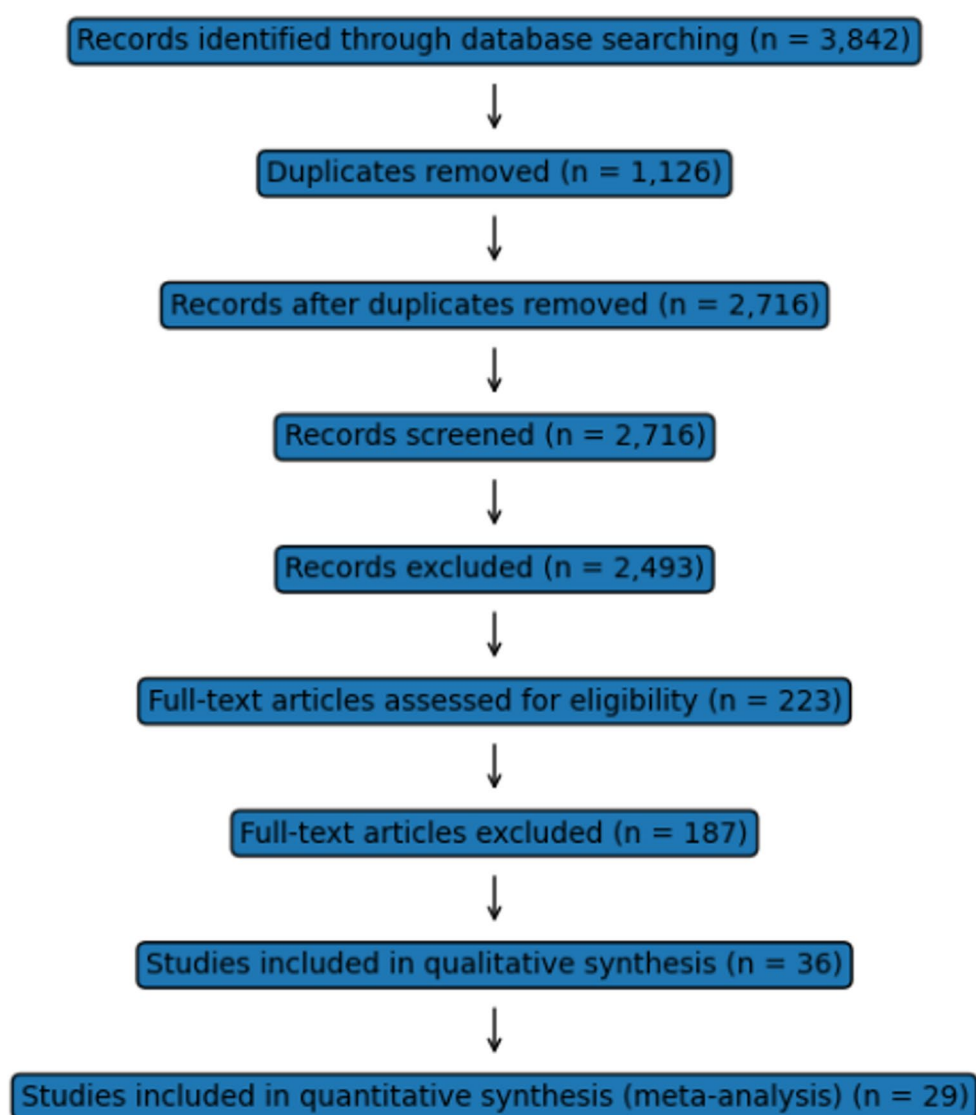
Quantitative CT biomarkers that were measured were lesion volume, midline shift, basal cistern compression indices, ventricular volume ratios, hematoma density, and composite quantitative CT scores. The CT scans that are not contrasted in all studies were carried out within the range of 6–72 h after the injury.

The outcome measures included an unfavorable neurological outcome, which was mainly a Glasgow Outcome Scale score of 3 or below and mortality, at hospital discharge, or a 30-day to 12-month follow-up.

Risk of bias assessment

The risk-of-bias assessment was considered low-risk, moderate-risk, and high-risk in 19, 12, and 5 studies, respectively. These were common examples of bias; non-consecutive selection of patients, timing of outcome assessment could be varied, and lack of blinding of the outcome assessors to the CT results. Flow and timing bias were not high, which was due to standardized acute imaging windows.

Fig. 3 PRISMA 2020 flow diagram of study selection process for inclusion in the systematic review and meta-analysis of quantitative CT biomarkers in acute traumatic brain injury



Pooled effect estimates

In a meta-analysis of 29 studies (15,904 patients) it was demonstrated that quantitative CT biomarkers are strongly related to poor neurological outcome resulting in a pooled odds ratio (OR) of 2.41 (95% CI: 1.98–2.93) under a random-effect model. The heterogeneity between the study was moderate to high ($I^2 = 64\%$).

The strongest biomarkers that predict poor neurological outcome were lesion volume (OR = 2.88) and midline shift (OR = 2.36); basal cistern compression and ventricular ratios had a statistically significant but smaller effect.

Concerning mortality, pool analysis of 21 studies proved the significant correlation between adverse quantitative CT results and the risk of death (OR = 2.67, 95% CI: 2.113.38).

Heterogeneity and sensitivity analysis

The exclusion in the heterogeneity (I^2 was lowered to 48) but had no significant impact on the pooled effect estimate (OR 2.32, 95% CI 1.95–2.77) when high-risk-of-bias studies were excluded; this strengthens result of robustness. The leave-one-out analyses did not reveal the presence of any one study that had disproportionate power.

Subgroup and meta-regression analyses

The subgroup analysis showed that the effect is stronger in severe-TBI cohorts (OR = 2.89) than in mixed severe ones (OR = 2.14). To the extent that CT scans were collected within 24 h after injury, the data showed a stronger correlation with the outcomes, which may indicate the early burden of injury and not necessarily causation.

The meta-regression revealed that the patient age ($p=0.03$), percentage of severe TBI ($p=0.01$), CT timing ($p=0.04$), and type of biomarkers ($p=0.02$) are all significant moderators with around 41% between-study variance.

Discussion

Interpretation of pooled outcomes

The systematic review, meta-analysis, and meta-regression provide evidence that quantitative CT biomarkers have a significant correlation with the early neurological outcome and mortality in patients with an acute traumatic brain injury (TBI). Combined studies demonstrated that objective CT-based measures, especially the size of lesions, the magnitude of the midline shift, and the measures of basal cistern compression place a person at risk of adverse neurological outcome and death two to three times more. This finding was strong even in sensitivity analyses and it was also consistent in neurological outcome and mortality endpoints, which provide the reliability of quantitative CT biomarkers as prognostic indicators.

The use of meta-regression further established a deeper explanation of the relationship whereby the prognostic value of quantitative CT biomarkers depends on patient age, the severity of injury, and the time of imaging. The outcome was found to be better predicted when the CT was obtained earlier (less than 24 h after injury) and produced a stronger effect, which shows the relevance of acute-phase imaging to reflect primary injury burden prior to the development of secondary pathophysiological mechanisms. Notably, volumetric biomarkers always showed higher predictive capacity than either linear or density-based measures, indicating that three-dimensional quantification can be better used to portray the scope of traumatic parenchymal damage. Taken together, these results suggest that quantitative CT biomarkers do reflect the most important types of injury that could not be well represented by qualitative methods or categorical scoring systems.

Relevance to emergency radiology and early management

In terms of emergency radiology, the results of this study are of significant clinical interest. Non-contrast CT is the backbone of acute TBI assessment as it is fast, accessible, and has diagnostic accuracy. Implementation of quantitative CT biomarkers in emergency processes can provide a chance to improve the decisions related to early triage, risk stratification, and management without adding delays and extra imaging expenses.

There are semi-quantitative biomarkers that can facilitate the early detection of at-risk patients, who might require urgent neurosurgical attention, aggressive intracranial pressure checks or urgent transfer to a special trauma unit. Objective risk estimates based on CT would help in prioritizing critical care resources as well as making decisions about observation instead of escalation of care in overcrowded emergency departments. Moreover, quantitative measures offer repetitive measures, which minimise interobserver variation, which is a recognised weakness of the traditional interpretation of CT, especially when less experienced radiologists interpret during off-hours.

Quantitative information retrieval through routinely obtained CT scans has a high potential to be beneficial in the current trends in emergency radiology, such as automated image processing and decision support using artificial intelligence. Quantitative CT can also fill the gap between fast imaging and prognostication based on precision theories, allowing the radiologist to be more actively involved in multidisciplinary acute TBI care as shown in the recent diagnostic accuracy literature.

Comparison with established CT scoring systems

The ancient systems of classifying CT such as the Marshall, Rotterdam, and Helsinki scores have been used long enough to classify the extent of injury and outcome in TBI. Even though these systems may prove invaluable help as far as prognostic information is concerned, they are categorical and require a visual assessment based on a threshold. Marshall classification principally focuses on mass effect as well as presence of lesion although the scores of Rotterdam and Helsinki have incorporated additional features such as basal cistern status and intraventricular hemorrhage.

Outcomes of the existing meta-analysis show that quantitative CT biomarkers contain incremental prognostic information compared to these traditional scoring systems. Unlike categorical scores, quantitative biomarkers depict continuous data that may be used to quantify the minute variations in the burden of injuries, and the risk may be distinguished more precisely. The binary categories of presence or absence of lesions do not have the same level of granularity at the level of volume of lesions and measures of midline shift in millimeters or cubic centimeters.

In addition, the traditional scoring systems were developed several decades ago and may not be potentially reflective of current imaging capabilities or current clinical management models. Quantitative CT biomarkers can be administered as additions to the already existent scores so that objective and scalable measurements can be incorporated into composite prognostic models. The quantitative CT measurements could be employed to supplement the existing systems as opposed to addressing the systems already in place, which are more predictive when thrown together.

Strengths of the study

This study has several strengths. To begin with, it is one of the most comprehensive syntheses that have been constructed so far that specifically considers the quantitative CT biomarkers in acute TBI. This review has bridged a large gap in the literature that general reviews of prognostics have introduced by restricting inclusion to studies which give numerical CT-derived parameters.

Second, the meta-regression allowed to conduct the systematic study of heterogeneity, which identified clinically important modifiers of prognostic performance. This approach to analysis renders pooled estimates more interpretable and more useful in the clinical context. Third, the adherence to PRISMA rules and risk-of-bias assessment with the assistance of QUADAS-2 and NOS tools and other sensitivity analyses prove the methodological strength of findings.

Finally, the externality of the findings to different health-care setups is increased by the variety of geographic locations and TBI severity spectrums.

Limitations

These are several constraints that should be mentioned. Heterogeneity of included studies was also high since it states that included studies were differentiated by the study design, imaging modalities, outcome measures, and follow up time. Although meta-regression explained a large proportion of between-study variance, the remaining heterogeneity remained, as it should in the prognostic imaging studies.

Further, most of the studies included were observational ones, which limited causal inference. The illogicality of variation in the effect sizes that have been reported could have been because of the variation in CT measure techniques and the non-standardization of the threshold of the quantitative biomarkers. Though this is not statistically significant, one cannot rule out publication bias.

Finally, although the findings showed that quantitative CT biomarkers are prognostic, these biomarkers could not be compared directly to the presented scoring systems because of the uneven reporting of studies.

Future directions and clinical translation

Future research should focus on how to standardize the definitions of quantitative CT biomarkers, how to validate automatized measurement tools, and prospective trials that embody quantitative CT measures into clinical decision algorithms. Potentially more accurate could be multimodal prognostic models which are developed by using the joint effect of quantitative CT biomarkers and clinical, laboratory, and physiological data.

As far as the translation of the quantitative CT analysis is concerned, the practice of making quantitative CT analysis a part of the everyday routine of emergency radiology is both a good and valid method of accuracy in the set of neurotrauma care. As more computational tools continue to be used, quantitative CT biomarkers will cease being a tool of research and become a common clinical tool.

Conclusion

This systematic review, meta-analysis, and meta-regression suggest that quantitative computed tomography (CT) biomarkers provide clinically meaningful and consistent prognostic associations with early neurological outcomes and mortality in patients with acute traumatic brain injury (TBI). Objective CT-derived measures—particularly lesion volume, degree of midline shift, and indices of basal cistern compression—were significantly associated with adverse outcomes across pooled analyses. These associations remained stable in sensitivity, subgroup, and meta-regression analyses, supporting the robustness of the findings across different study designs and patient populations.

From a clinical perspective, quantitative CT measurements offer objective and reproducible metrics that may enhance characterization of injury burden beyond purely qualitative interpretation. Compared with categorical scoring approaches, continuous quantitative parameters allow more granular representation of structural damage. Volumetric and multi-parameter biomarkers demonstrated larger pooled effect sizes than linear or threshold-based measures, suggesting that comprehensive quantification of injury extent may better reflect outcome-associated structural changes.

Within emergency radiology practice, quantitative CT biomarkers have potential translational relevance. Because non-contrast CT is already central to acute TBI assessment, extraction of structured quantitative information from routinely acquired scans may support early risk stratification and multidisciplinary clinical discussions without requiring additional imaging. These measures may assist communication among treating teams and contribute to more structured prognostic assessment in acute care environments, particularly as automated image-processing and decision-support systems continue to evolve.

Importantly, quantitative CT biomarkers should be viewed as complementary to established CT-based scoring systems, including the Marshall CT classification, Rotterdam CT score, and Helsinki CT score. While quantitative measures provide continuous and potentially scalable metrics, they are not substitutes for traditional classifications without prospective validation and external calibration. Rather, they may serve as components of future integrative prognostic frameworks combining imaging, clinical, and physiological data.

In summary, quantitative CT biomarkers represent a promising direction in early outcome assessment following acute TBI. Their demonstrated associations with clinically relevant endpoints, compatibility with existing imaging workflows, and potential integration with emerging computational tools support continued investigation. Further standardization of measurement protocols and prospective multicenter validation studies are necessary before broader clinical implementation.

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Data Availability The extracted datasets used for meta-analysis are available from the corresponding author upon reasonable request.

Declarations

Consent for publication Not applicable.

Consent to participate Not applicable.

Conflict of interest The authors declare no conflict of interest.

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