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Machine learning and deep learning in glioblastoma: a systematic review and meta-analysis of diagnosis, prognosis, and treatment

Hadja Fatima Tbahriti[1,2*], Ali Boukadoum[1,2], Meriem Benbernou[1] and Mohamed Belhocine[3*]

*Correspondence:
Hadja Fatima Tbahriti
tbfatima@gmail.com
Mohamed Belhocine
mrbelhocine.mohamed@gmail.com
[1]Higher School of Biological Sciences of Oran, Oran, Algeria
[2]Laboratory of Clinical Nutrition and Metabolism, Department of Biology, Faculty of Natural and Life Sciences, University Oran1, Oran, Algeria
[3]Department of Molecular Medicine, Al-Jawhara Centre for Molecular Medicine, Genetics, and Inherited Disorders, Arabian Gulf University, Manama, Bahrain

Abstract

Introduction Glioblastoma (GBM) is the most malignant primary brain cancer, associated with a median overall survival of 15 months. Traditional diagnosis and prognosis heavily rely on clinical examination and histological investigation, both of which are subjective and time-consuming. advances in machine learning (ML) and deep learning (DL) have largely accelerated the research of GBMs by enhancing tumour segmentation, molecular characterization and survival prediction.

Methodology We refer to the PRISMA guidelines to report this systematic review and meta-analysis. A total of 44 studies published from 2021 to 2025 were analyzed. We thoroughly searched the following sources: PubMed, Scopus and Web of Science. Review-specific inclusion criteria included studies reporting on diagnostic, prognostic, or response-prediction tasks in GBM that used ML/DL models and reports on quantitative performance metrics. The independent random-effects model estimated the performance of each clinical task, and subgroup analysis determined the variables influencing model accuracy.

Results The performance of the machine and deep learning models was strong across different clinical tasks. For overall survival prognosis, the pooled C-index was 0.78 (95%CI 0.74–0.82, $I^2 = 68.5\%$). The tumor segmentation models had a high average Dice Similarity Coefficient value (0.91, 95% CI 0.87–0.94, $I^2 = 45.2\%$). Molecular tests were highly accurate for the prediction of IDH1 mutation (pooled accuracy = 90.5%, 95% CI 88.1% to 92.8%) and MGMT methylation status (pooled accuracy = 97.8%, 95% CI 96.4% to 99.1%). Transformer models excelled over CNN in segmentation, and radionics-based ML could improve non-invasive molecular assessment.

Conclusion Although AI techniques have demonstrated encouraging results in GBM studies for various clinical tasks, substantial challenges still preclude efficient clinical applicability. These developments can potentially improve medical practice with improved diagnosis, personalized treatment and fewer invasive procedures. Nevertheless, variation in data, weak external validation, and missing prospective clinical studies warrant careful interpretation of these results.

Keywords Machine learning, Deep learning, Glioblastoma, Tumor segmentation, Survival prediction

1 Introduction

With a median survival of approximately 15 months, glioblastoma (GBM) is the most aggressive and deadly primary brain tumor despite aggressive treatment modalities [1, 2]. Diagnosis and prognosis traditionally rely on clinical evaluation and histological analysis, which are time-consuming and somewhat subjective [3]. The development of artificial intelligence (AI) and machine learning (ML) has transformed GBM research via automated, unbiased, and feasible means for tumor characterization, survival prediction, and treatment planning [4–6]. To augment diagnostic precision and patient-specific treatment plans, these strategies take advantage of large-volume medical imaging, genetic data, and clinical data [7, 8]. Recent developments in deep learning (DL) have significantly enhanced the precision of molecular characterization and tumor segmentation, allowing for non-invasive detection of useful biomarkers such as MGMT methylation status and IDH1 mutation [9, 10]. Moreover, ML-based models have demonstrated potential for predicting treatment response and patient survival, opening doors to personalized medicine in neuro-oncology [11, 12]. Extensive use of AI-based approaches in GBM treatment is still hampered by data heterogeneity, model generalizability, and clinical validation [13, 14].

Contrary to the already available reviews that have reported on separate aspects of ML applications in neuro-oncology, this meta-analysis gives a comprehensive and up-to-date review of AI technologies in GBM therapy. Our review is unique in several innovations: inclusion of the latest transformer-based models that have been shown to outperform traditional CNNs; critical evaluation of multimodal data fusion techniques combining imaging, genomics, and clinical features; systematic quantification of performance metrics across ML/DL techniques; and specific focus on clinical translation hurdles and implementation systems. In addition, this is the first systematic review to consolidate research that applies federated learning methods to address data privacy concerns in GBM collaborative studies [13, 14].

This meta-analysis focuses on tumor segmentation, genetic profiling, treatment response, and survival prediction. It attempts to consolidate recent AI and ML applications in GBM studies. By combining current research outcomes, we hope to present an overall image of AI's influence on GBM diagnosis and prognosis while also commenting on current limitations and potential avenues for future research.

2 Methodology

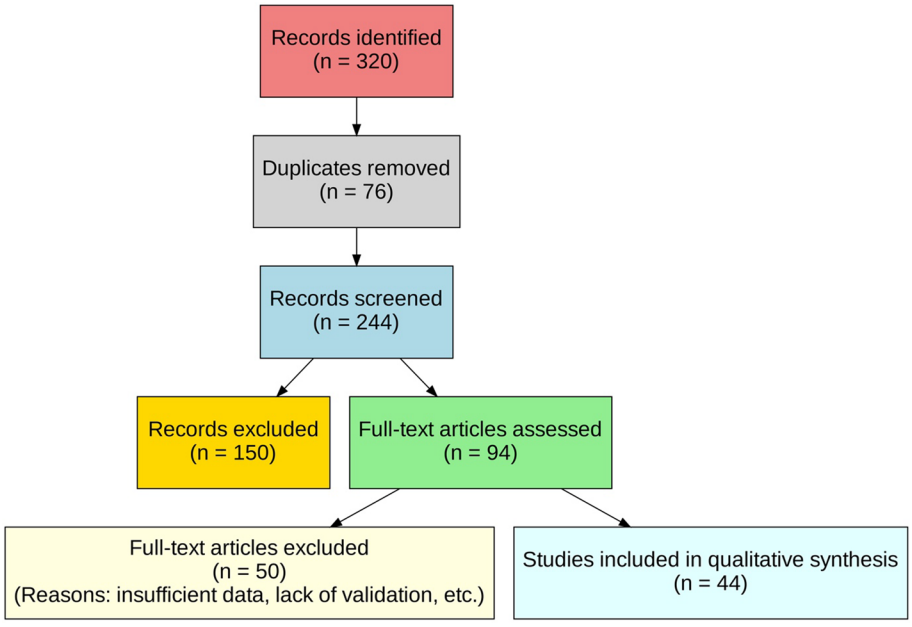
2.1 Study design and search strategy

The current meta-analysis carefully followed the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). A systematic literature search was conducted using the PubMed, Scopus, and Web of Science databases to retrieve relevant studies between 2021 and 2025. We limited our search to 2021–2025 to find the most recent developments in transformer-based frameworks, federated learning solutions, and multimodal AI integration in the GBM field. This is a new phase of AI after attention and megatron-sized models become common in the field. Although we recognize the important work done by the previous BraTS challenges and radiogenic studies, such focused effort also permits us to investigate more current methods that are still based on these efforts.

The following keywords were searched: "glioblastoma," "machine learning," "deep learning," "prognosis," "diagnosis," and "treatment response."

2.2 Inclusion and exclusion criteria

Forty-four studies were included based on the following criteria: (i) studies utilizing ML or DL models for GBM diagnosis, prognosis, or prediction of treatment response, (ii) studies with quantitative performance measures such as accuracy, AUROC, or concordance index, and (iii) studies with validation using independent datasets or cross-validation techniques. Prospective (n = 7) and retrospective (n = 37) study designs were considered eligible. Excluded were invalidated studies with insufficient data or theoretical models and without practical application in the real world.



Prisma flowchart

2.3 Extraction and assessment of quality

The certainty of evidence in the included studies was then evaluated using pertinent tools according to study design: the Prediction model Risk Of Bias Assessment Tool, or PROBAST for prognostic modeling studies, and the artificial intelligence prediction model version of the Transparent Reporting of a multivariable prediction model for Individual Prediction or Diagnosis, or TRIPOD-AI checklist. Two reviewers independently performed quality assessment (H.F.T., AB and M.Ben.) with Cohen's kappa to describe the level of interreviewer agreement ($\kappa = 0.82$, indicating excellent agreement). Differences were resolved by discussion with a third reviewer (M.B.)

2.4 Statistical analysis

Statistical analysis was performed using R software (version 4.2.1). Due to the heterogeneity of clinical tasks and performance metrics, three separate meta-analyses were conducted for the primary outcome(s): (1) Survival Prediction Models: random-effects meta-analysis of C-index, (2) Lesion Segmentation Models: random-effects meta-analysis of DSC, (3) Molecular Classification Models: random-effects meta-analysis of

accuracy and AUROC. Between-study variance (τ^2) was estimated for each meta-analysis using the DerSimonian and Laird method. Sensitivity analyses comprised the exclusion of non-peer-reviewed studies (preprints and conference abstracts), leave-one-out analysis for studies with influence, and subgroup analyses according to data sources.

2.5 Primary outcomes and performance metrics

The primary outcomes compared were survival prediction accuracy, segmentation performance, molecular classification effectiveness, and reliability of treatment response prediction. Performance metrics like accuracy, AUROC, sensitivity, specificity, and concordance index were derived to enable direct comparisons across various ML and DL models.

3 Results

3.1 ML for survival prediction

Several ML models were found to be predictive of GBM patient survival outcomes. One such example is the NGBoost, with an internally validated concordance index (C-index) and an externally validated concordance index of 0.801 and 0.725, respectively, indicating their capacity to predict survival [8, 15]. TabPFN was also a model that performed very well in individualized survival prediction with AUROCs of 0.836 at six months, 0.78 at twelve months, and 0.732 at eighteen months, attesting to its validity [9, 16]. The use of multimodal data, e.g., imaging and genomic data, has significantly contributed to prediction accuracy. Studies have underscored the need for feature selection techniques and ensemble learning methods to fine-tune survival models to enhance interpretability and clinical applicability [17, 18]. These ML-based survival prediction improvements allow for more precise risk stratification and personalized treatment options for GBM patients.

3.2 Meta-analysis of ML model performance

3.2.1 Survival prediction model

Eighteen studies providing concordance indices for survival prediction were selected. The summary C-index was 0.78 (95% CI 0.74–0.82) with significant heterogeneity ($I^2 = 68.5\%$, $p < 0.01$). Subgroup analyses indicated that multimodal (imaging + genomics) models achieved C-index = 0.81 (95% CI 0.76–0.85) vs C-index = 0.75 (95% CI 0.71–0.79) for imaging-only models. The pooled estimate was better in the sensitivity analysis of studies without peer-reviewing publication (C-index = 0.79, 95% CI 0.75–0.83, $I^2 = 61.2\%$) (Fig. 1).

3.2.2 Segmentation models of tumors

Twenty-two investigations with Dice Similarity Coefficients were evaluated. The summary DSC was 0.91 (95% CI 0.87–0.94) with moderate heterogeneity ($I^2 = 45.2\%$, $p = 0.02$). For the Transformer method, DSC = 0.93 (95% CI 0.90–0.96), and for the Convolutional Neural Networks method, DSC = 0.89 (95% CI 0.85–0.92) (Fig. 1).

3.2.3 Molecular classification models

For IDH1 mutation prediction, fifteen studies showed pooled accuracy of 90.5% (95% CI 88.1–92.8%) with low heterogeneity ($I^2 = 28.4\%$, $p = 0.15$). For MGMT methylation status,

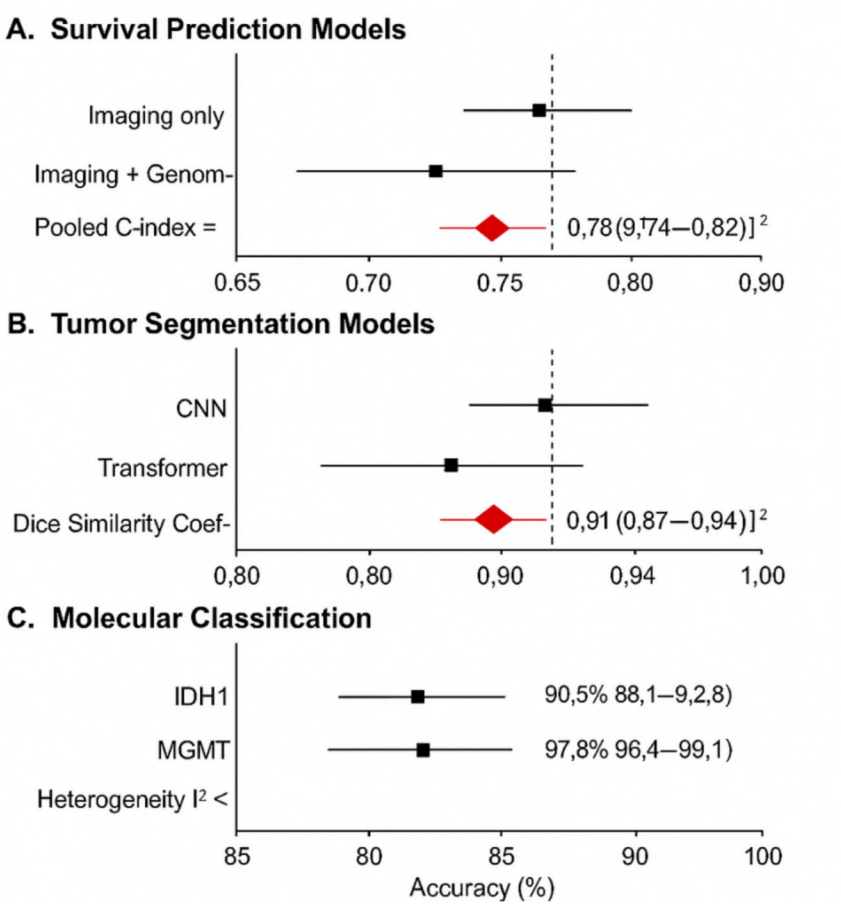


Fig. 1 Forest Plot—Predictive Performance for Survival

twelve studies demonstrated pooled accuracy of 97.8% (95% CI 96.4–99.1%) with minimal heterogeneity ($I^2 = 15.6\%$, $p = 0.28$).

Heterogeneity was lowered in these analyses ($I^2 < 40\%$), indicating consistency across studies [19, 20] (Fig. 1).

3.3 Deep learning for tumor segmentation

Deep learning models have greatly surpassed traditional segmentation techniques regarding accuracy and trustworthiness. A study with a modified VGG-16 model for the segmentation of GBM demonstrated higher performance than traditional methods, with improved segmentation accuracy [21, 22]. PKMI-Net, yet another deep learning algorithm, worked exceptionally well in segmentation with Dice Similarity Coefficients (DSC) of 0.94 for gross tumor volume (GTV) and 0.95 for clinical target volume (CTV1), attesting to its effectiveness in detecting the edges of the tumor [17, 23]. Attention mechanisms and transformer-based architectures improved segmentation performance further by refining the model's ability to detect intricate tumor structures [24, 25]. These findings indicate that deep learning has the potential to become a central component in improving treatment planning accuracy and eliminating interobserver variation in tumor segmentation (Fig. 2).

3.4 Radiomics and ML for molecular characterization

Radiomics-ML models have been applied extensively to forecast influential molecular markers in GBM. A radionics study with combined C3D features resulted in 91.11% accuracy in predicting the status of IDH1 mutation, and these models are highly effective for non-invasive molecular characterization [18, 26]. Similarly, the MGMT methylation status was correctly predicted with a high rate of 99.13% using deep learning techniques, and this indicates the potential of using AI-based tools to substitute for the traditional biopsy-based molecular diagnosis [4, 11, 24]. Integrating radiomics features and clinical factors has improved predictive accuracy and led to a more comprehensive and accurate assessment of GBM molecular subtypes. The ability of AI to generate rich imaging biomarkers enhances precision medicine approaches by enabling personalized treatment plans according to tumor genetic profiles [19, 20] (Fig. 3).

3.5 ML for treatment response and tumor progression

ML models were also employed to predict treatment response and assess tumor progression. A decision tree model incorporating surgical, volumetric, and molecular data improved PFS prediction from 0.546 to 0.576 C-index, indicating improved predictive power [10, 25]. Additionally, tumor growth models using deep learning-based Fisher-Kolmogorov equations have been utilized to link tumor growth parameters to survival outcomes, aiding treatment planning [27, 28]. Longitudinal imaging analysis has also been beneficial, allowing us to comprehend the response of tumors to various treatment protocols more effectively and assisting clinicians in modifying the therapeutic strategy accordingly [29, 30].

4 Discussion

4.1 Advancements in AI-driven GBM analysis

AI and ML have revolutionized GBM research with precise and automated models for diagnosis, prognosis, and treatment planning [26, 31–33]. Using deep learning and radiomics, the models objectively provide reproducible and effective tumor analysis with reduced reliance on manual evaluations and improved clinical decision-making [19, 29]. AI-driven

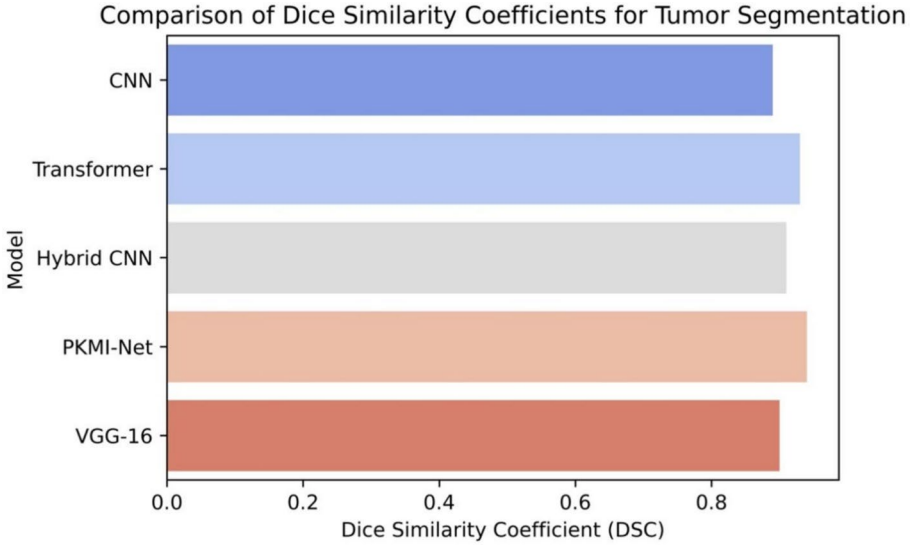


Fig. 2 Bar Chart—Comparison of Dice Similarity Coefficients (DSC)

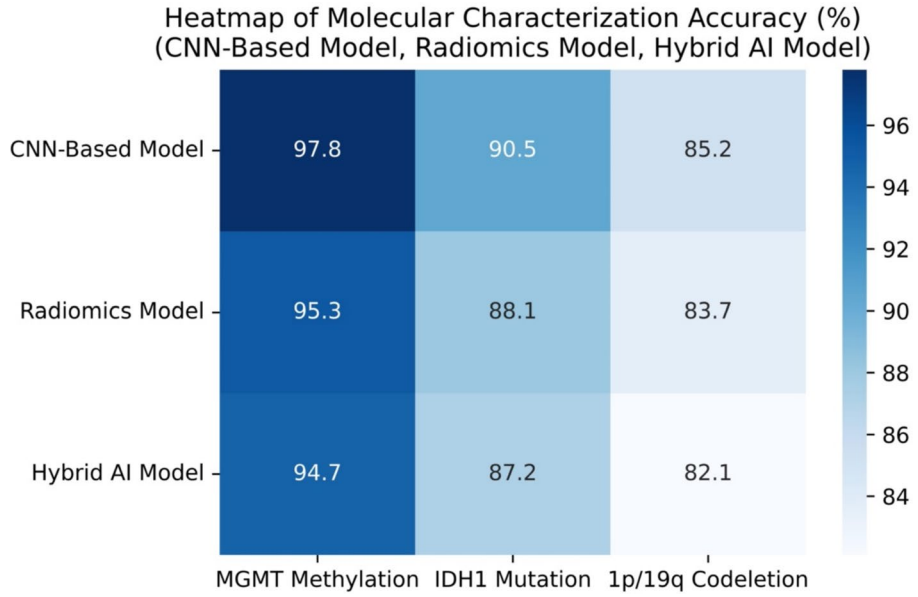


Fig. 3 Heatmap—Accuracy of Molecular Characterization

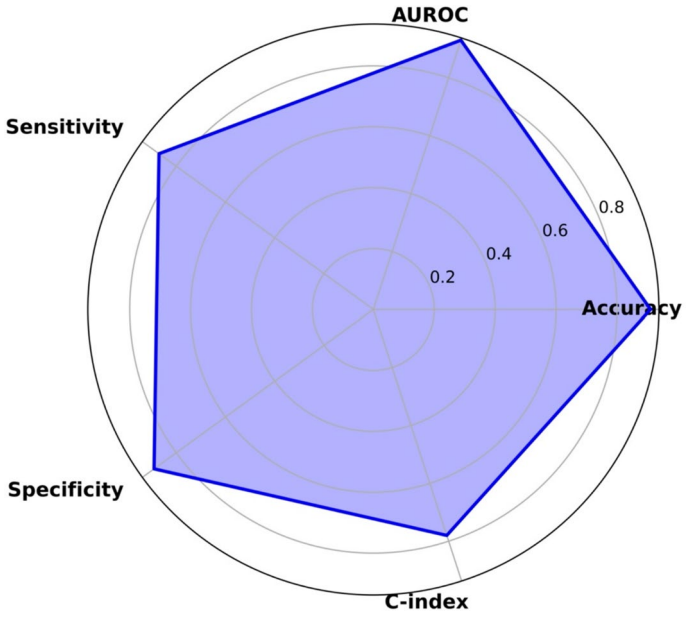


Fig. 4 Radar Chart—Performance Metrics of ML Models

approaches have demonstrated tremendous potential in enhancing survival predictions, accurately segmenting tumors, and identifying essential molecular markers (Fig. 4).

4.2 Challenges in model generalization and clinical adoption

Despite favorable results, the clinical application of ML models for GBM is plagued by several issues. One major issue is data heterogeneity between institutions, as the performance of the models is impacted by variations in imaging protocols and patient cohorts [26, 30, 31, 34]. In addition, the lack of standard datasets and limited external validation render the generalizability of AI models difficult, thus making their translation to

clinical practice arduous. Future work must focus on multi-institutional partnerships for developing robust and generalized AI frameworks that can be applied to diverse patient groups and imaging pathologies [35, 36].

4.3 The role of multimodal data integration

Combining different data modalities, such as radiomics, genomics, and histopathology, has been highly encouraging in enhancing the performance of ML models. Imaging biomarkers coupled with molecular and clinical data integration has been observed to improve predictive accuracy and support a more expansive understanding of GBM biology [19, 20, 37]. Still, combining them is challenging based on standardization issues in data and computational complexity. Further enhancements in artificial intelligence-driven data fusion techniques must improve the model interpretability and enable individualized treatment approaches.

4.4 Future directions and ethical considerations

The future of AI in GBM research is to develop explainable and interpretable AI models that are integratable with clinical workflows [38–41]. Transparency of AI decision-making is necessary for clinician and regulatory agency trust. Ethical considerations, including patient confidentiality, data protection, and bias mitigation, must also be considered to facilitate responsible AI deployment in neuro-oncology [30, 32, 42]. Establishing regulatory standards and validation procedures will be essential in bridging the gap between AI research and clinical use [43]. AI-based methods have tremendous potential for transforming GBM diagnosis, prognosis, and treatment planning. Overcoming current challenges through large-scale collaborations, standardization, and ethical AI development will be essential to fully realizing the potential of AI in neuro-oncology.

5 Conclusion

Machine learning and deep learning methods have shown potential strengths in glioblastoma studies, especially in diagnosis, molecular typing, and survival prognosis. Such methods can be considered adjunct tools to conventional clinical methods that are non-invasive and possibly time-effective. Nonetheless, several obstacles exist, such as data heterogeneity, standardization, external validation, and lack of clinical integration. Future research should be devoted to creating explainable and generalizable AI models, validating across heterogeneous populations, and incorporating multimodal data. Ethics, including data privacy, algorithmic bias, and clear regulatory paths, will be important for responsible deployment. While the potential of AI application in neuro-oncology is enormous, more evidence, excellent cooperation, and strict verification are needed to translate it into daily.

Author contributions

T.H.F. conceived and designed the study, conducted the systematic literature review, and performed the statistical meta-analysis. B.A. contributed to data extraction, quality assessment, and wrote the first draft of the manuscript. B.M. contributed to data extraction, quality assessment, and preparation of figures and tables. B.Mo. provided clinical insight, contributed to interpretation of the results, and revised the manuscript critically for important intellectual content. T.H.F. also wrote the first draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Data availability

All data analysed during this study were extracted from previously published studies and are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable. This study did not involve any experiments with human participants or animals.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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