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Review Article

Explainable Artificial Intelligence (XAI) for Personalized Prognosis and Treatment Optimization in Glioblastoma

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Abstract

Glioblastoma multiforme (GBM) is one of the most aggressive primary glioma brain cancer in adults that has poor prognosis and few medications. Recent developments in Explainable Artificial Intelligence (XAI) have made it possible to develop clinical-interpretable predictive models with high accuracy to help with personalized prognosis and optimization of treatment. This systematic review and meta-analysis summarize the existing research studies on the XAI-based models of GBM prediction and management published between 2020-2025. The study used multiple database search to identify eligible studies that were further screened with pre-determined inclusion criteria. Important performance measures such as area under the curve (AUC) and accuracy were retrieved and interpreted descriptively. The findings show that well-performing machine learning models, including XGBoost, deep neural networks, and ensemble models, produce AUCs as high as 0.9845 and accuracies as high as 95.5%. The most common prognostic factors identified with the use of XAI techniques like SHapley additive exPlanations and local interpretable model-agnostic explanations were IDH1 mutation status, patient age, radiomic texture factors, and therapeutic regimens. In other instances, novel biomarkers, including one representing PPP2RIB identified by PathX-convolutional neural networks were discovered, showing the promise of XAI to reveal new clinical knowledge. Nevertheless, there are limitations to these advances, such as class imbalance, the need for multi-modal dataset combining radiomics and genomics, and lack of standardized integration protocols with clinical care.

Categories: Algorithm Analysis, Explainable AI, Computational Science and Engineering

Keywords: glioblastoma, cancer, explainable ai, machine learning, survival prediction, prognosis, shap, lime

Introduction And Background

Glioblastoma multiforme (GBM) has been identified as one of the most virulent of primary malignant brain tumors that are very difficult to diagnose and treat. It is a poor prognosis disease with median survival rates of 12-15 months in newly diagnosed patients and even less in recurrent cases of the disease, of about 5-7 months [1,2]. These values underline the necessity of efficient therapeutic approaches since GBM is a deadly disease and has many complications.

A combination of surgery, radiotherapy, and chemotherapy, mostly temozolomide is the standard of care of GBM [3,4]. Although these methods have demonstrated potential of survival extension, recurrence of the disease after treatment is distressingly high and the majority of patients develop a tumor recurrence within 2 years following the initial treatment [5]. The results of observational studies in the National Cancer Database show a median survival of only 7.5 months under real-world conditions, which are considerably lower than those in the controlled clinical trials [6]. This variance highlights the possible difference that access to care and the efficacy of the treatment modalities may have in various healthcare

environments.

The underlying biological heterogeneity of GBM is a primary reason why this disease has adverse prognosis and difficulty in treatment. This heterogeneity is present at a genetic and phenotypic level making it possible to have varied subpopulations of tumor cells capable of producing treatment resistance [7,8]. As an example, glioblastoma stem cells (GSCs) have been put forward as a possible source of therapeutic resistance, being able to survive standard therapies and causing a tumor repopulation following initial treatments [9,10]. Moreover, the blood-brain barrier makes drug delivery difficult because most potential treatments fail to reach the brain effectively [11].

In addition, recent developments in GBM comprehension have indicated that immunosuppressive processes in the tumor microenvironment compromise the efficacy of immunotherapies [12,13]. Although there have been advancements in the development of drugs and the possibilities of new treatments to target key mechanisms in the proliferation and survival of tumors, the clinical use of these drugs has not led to significant overall survival outcomes among patients [14,15]. For example, anti-vascular treatments have attracted much interest, but have been of limited success, prompting a reconsideration of treatment paradigms [16,17].

The use of artificial intelligence (AI) and machine learning (ML) in oncology has been extremely promising in changing the methods of detecting, diagnosing, and treating cancer. The application of AI technologies has recently improved to allow fast processing of high volumes of data to facilitate the making of informed decisions by clinicians based on patterns in patient information, imaging, and genomic data [18,19]. This transformation is especially significant in the sphere of digital pathology, where AI can be applied to analyze complicated datasets and, thus, make a patient diagnosis more accurate and lead to better patient outcomes [20].

AI's applications in oncology have expanded significantly as tools for risk stratification, treatment prediction, and personalized therapy. Radiological-image-analysis algorithms have the potential to recognize the features of the tumor and forecast the development of the disease, which allows them to receive individual treatment procedures [19]. One of the most important parts of this development is the emergence of deep learning (DL) methods which employ the use of neural networks to automatically derive features within images, which might not be easy to see through human eyes [20,21]. The use of AI-driven tools enhances the efficiency of workflow and diagnostic accuracy, which is an indicator of a paradigm shift in oncological care delivery.

However, despite these advancements, the incorporation of AI in clinical settings presents challenges, notably the "black-box" nature of many AI systems. AI systems especially those that are DL-based, tend to work in opaque ways and clinicians may not be able to decipher how a recommendation was made or a diagnosis given. Such interpretability can present a problem of accountability and trust in the context of healthcare practitioners, where practitioners may be hesitant to take the decisions made by opaque algorithms [22,23]. The black-box problem makes the validation of AI applications in the real clinical practice more complicated and raises ethical concerns about patient safety and informed consent [24,23].

The ability to have interpretable and transparent AI applications in oncology is critical to the successful incorporation of these applications in practice. This current research focuses on reviewing studies on explainable AI systems that can give clinicians an idea of how the model works, allowing them to confirm and potentially question AI-driven suggestions [22,24]. There is a possibility to improve the adoption of AI in the design of models that are interpretable by humans, which would improve acceptance and create a collaborative space where clinicians and technology integrate to offer the best care to patients [18,24].

Review

Literature review

Current State of Explainable Artificial Intelligence in Oncology

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The integration of Explainable Artificial Intelligence (XAI) into oncological practice represents a paradigm shift from traditional black-box ML models toward transparent, interpretable systems capable of providing clinically meaningful insights. Several recent studies have demonstrated the potential of XAI approaches in improving GBM prognosis and treatment optimization, though significant methodological and translational challenges persist [25,26]. Holzinger et al. [27] introduced the concept of "causability" as a critical framework for evaluating AI explanations in medical contexts, emphasizing that explainability must extend beyond technical feature importance to establish causal relationships that clinicians can trust and act upon. This framework has been instrumental in shaping recent XAI research in neuro-oncology, where the complexity of tumor biology demands sophisticated interpretative approaches. Lambin et al. [28] further demonstrated that radiomics serves as a crucial bridge between medical imaging and personalized medicine, providing quantitative features that, when combined with XAI techniques, can reveal clinically actionable insights.

Comparative analysis of XAI methodologies

The reviewed studies employed diverse XAI methodologies, each with distinct advantages and limitations. SHapley Additive exPlanations (SHAP) emerged as the most frequently utilized technique across the included studies [29-38], likely due to its solid theoretical foundation in game theory and ability to provide both global and local explanations. However, comparative analyses reveal important methodological differences in implementation.

Palkar et al. [31] employed multiple XAI techniques [SHAP, local interpretable model-agnostic explanations (LIME), ELI5, and QLattice] in conjunction with various ML classifiers for glioma grading, finding that while SHAP consistently identified IDH1 mutation status as the most critical prognostic feature across all models, LIME provided more stable local explanations for individual predictions. This finding aligns with broader literature suggesting that ensemble XAI approaches may offer more robust interpretability than single-method applications.

In contrast, Alahakoon et al. [33] utilized SHAP exclusively for interpreting Random Forest models predicting overall survival from radiomic features, demonstrating that SHAP interaction values could reveal complex feature interactions not apparent through univariate analysis. Their approach identified risk inflexion points in key radiomic features, providing clinically actionable thresholds for treatment decision-making.

Methodological limitations and research gaps

Critical analysis of the current literature reveals several significant limitations that must be addressed to facilitate clinical translation. First, the majority of included studies employed retrospective designs with relatively small sample sizes (ranging from 77 to 347 patients for GBM-specific studies), raising concerns about selection bias and generalizability [33,38]. The study by Sadeghinasab et al. [38], while methodologically rigorous, included only 77 GBM patients, limiting the statistical power to detect meaningful associations.

Second, significant heterogeneity exists in XAI evaluation frameworks. While most studies reported standard performance metrics (AUC, accuracy), fewer provided comprehensive assessments of explanation quality or clinical utility. The lack of standardized benchmarks for evaluating XAI interpretability in oncology represents a critical gap, as highlighted by D'Amiano et al. [22] in their scoping review of transparency in AI-driven oncology research.

Third, external validation remains uncommon across the reviewed studies. Only Teng et al. [35] performed external validation using a separate cohort, demonstrating that model performance can degrade significantly when applied to different populations. This finding underscores the importance of multi-institutional validation studies prior to clinical deployment.

Synthesis of key prognostic factors

Despite methodological limitations, consistent patterns emerge regarding key prognostic factors identified through XAI techniques. IDH1 mutation status was uniformly identified as the strongest predictor across studies incorporating molecular data [31,36], consistent with established clinical knowledge and validating the biological relevance of XAI-derived insights. Age at diagnosis emerged as the second most important predictor [29,32,37], with SHAP dependency plots revealing non-linear relationships that may inform treatment decisions for elderly patients.

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Novel insights were also generated through XAI analysis. The PathX-convolutional neural network (CNN) framework developed by Sobhan et al. [34] identified PPP2R1B as a previously underappreciated prognostic gene, demonstrating the potential for XAI to generate new biological hypotheses. Similarly, radiomic features related to tumor texture and heterogeneity showed consistent associations with survival outcomes [33,38], suggesting that quantitative imaging biomarkers may complement traditional clinical and molecular prognostic factors.

Clinical translation challenges

The transition from research prototypes to clinically deployed XAI systems faces substantial barriers. Kolla and Parikh [19] identified algorithmic bias and dataset diversity as critical concerns, noting that models trained on homogeneous populations may perform poorly when applied to underrepresented groups. This concern is particularly relevant for GBM, where molecular subtypes vary across demographic groups.

Furthermore, the integration of XAI tools into clinical workflows requires careful consideration of user interface design, explanation formatting, and decision support protocols. As noted by Rios et al. [13] in their review of emerging GBM therapies, technological innovation must be accompanied by implementation science to realize clinical impact. Future research should prioritize prospective clinical trials evaluating XAI-enhanced decision-making against standard care, with endpoints that include both clinical outcomes and measures of clinician trust and satisfaction.

Methods

This is a systematic review and meta-analysis study conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [25]. The review protocol was prepared a priori, which guarantees methodological transparency and replicability. All review processes were based on PRISMA guidelines and best evidence synthesis in biomedical informatics and AI in healthcare.

The review aims at finding and synthesizing the studies using XAI methods in the process of prognosis and treatment optimization of GBM. The consistency of the screening, extraction, and synthesis process was achieved through the use of a structured search strategy, predefined inclusion/exclusion criteria, and standardized data extraction forms.

This study selection process is illustrated in Figure *1*, which presents the PRISMA 2020 flow diagram showing the number of records identified, screened, and included in this systematic review.

Eligibility criteria

To ensure the relevance and quality of the included studies, specific inclusion and exclusion criteria were established based on the Population, Intervention, Comparison, Outcome, and Study Design (PICOS) framework [26].

PICOS Framework

P - Population: Patients diagnosed with glioblastoma/cancer (GBM), regardless of age, sex, or geographic location. This includes individuals whose clinical, imaging, genomic, or multimodal data were used to build and validate AI models.

I - Intervention: Application of XAI techniques in AI/ML models aimed at prognosis prediction (e.g., survival time, recurrence risk) or treatment optimization (e.g., radiotherapy response, chemotherapy regimen selection). Examples include SHAP, LIME, attention mechanisms, rule-based systems, and inherently interpretable models.

C - Comparison: Traditional AI/ML approaches without explainability (black-box models), or different types of XAI approaches compared to each other, or baseline clinical decision-making methods (e.g., standard prognostic scoring systems).

O - Outcome: Predictive performance (AUC and accuracy) and the interpretability or explainability of the model outputs and clinical utility, trust and acceptance by clinicians, impact on decision-making, and potential for integration into clinical workflows.

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Inclusion criteria

The review included studies that met all of the following criteria:

1. Targeting GBM diagnosis, prognosis, or response to treatment, predictive or treatment planning.

2. Utilized XAI methods, e.g., SHAP, LIME, attention mechanisms, rule-based models, or more naturally interpretable models (e.g., decision trees, generalized additive models).

3. Treated individualized prognosis (e.g., prediction of survival time, risk of recurrence) and/or individualized treatment (e.g., choice and/or modification of therapy plans).

4. Used real-world data such as medical images, genomic data, clinical data, or multimodal data.

5. Available in peer-reviewed journals or proceedings and published in English.

Exclusion criteria

The review excluded studies that fell under one of the following reasons:

1. Did not consider or use an XAI technique (i.e., used black-box models without the ability to interpret).

2. Concentrated on creating algorithms and did not apply to GBM/cancer data.

3. Conducted on non-human subjects or in purely simulated environments.

4. Were review articles, editorials, commentaries, or protocol papers that lacked original data analysis.

5. Did not provide enough information to assess the model performance or explainability (e.g., did not provide model performance, XAI results, etc.).

Information sources and search strategy

The search was carried out in several scientific databases to find relevant studies. These databases were PubMed, IEEE Xplore, Scopus, and arXiv. The search was restricted to publications between January 2020 and July 2025 to find the recent progress in the field of XAI and its application to GBM research.

A combination of Medical Subject Headings (MeSH) and free-text terms in relation to glioblastoma, ML, and XAI were used to develop the search strategy. Boolean operators (AND, OR) were used to combine terms. A typical search string within PubMed is as follows:

("glioblastoma" OR "GBM") AND ("explainable AI" OR "interpretable machine learning" OR "XAI" OR "SHAP" OR "LIME" OR "attention mechanism" OR "explanation" OR "rule-based model") AND ("prognosis" OR "survival prediction" OR "treatment optimization" OR "treatment response" OR "personalized medicine") which gave 72 results on PubMed and 13 results on IEEE Xplore.

Study selection and data extraction

For each included study, data were extracted using a standardized data extraction form. Key data items included study identifiers, methodological details, AI/XAI techniques, and outcome measures. The extracted data were cross-validated for consistency and accuracy.

The following data items were extracted from each study:

• Study identifiers: Title and publication year

• Data type/Sample size: Imaging [e.g., magnetic resonance imaging (MRI)], genomics, histopathology, clinical variables, or multimodal, sample size, data source, clinical population.

• ML/DL type: DL [CNN, long short-term memory (LSTM)], traditional ML [support vector machine (SVM), random forest], ensemble models, etc.

• XAI method used: SHAP, LIME, Grad-CAM, attention mechanism, saliency maps, rule-based models, etc.

• Results/Findings: Prognostic (e.g., survival time, recurrence risk), therapeutic (e.g., response prediction, optimal regimen selection), model performance.

• Model performance metrics: Accuracy and area under the curve (AUC).

• Explainability evaluation: Qualitative or quantitative assessment of interpretability, clinical relevance of explanations.

Critical analysis of the included studies reveals several methodological limitations. The majority of studies employed retrospective designs with relatively small sample sizes, raising concerns about selection bias and generalizability. Furthermore, significant heterogeneity in XAI methodologies from SHAP and LIME to attention mechanisms precludes direct comparison across studies. The lack of standardized evaluation frameworks for interpretability assessment represents a major gap in the current literature (as illustrated in Figure *1*).

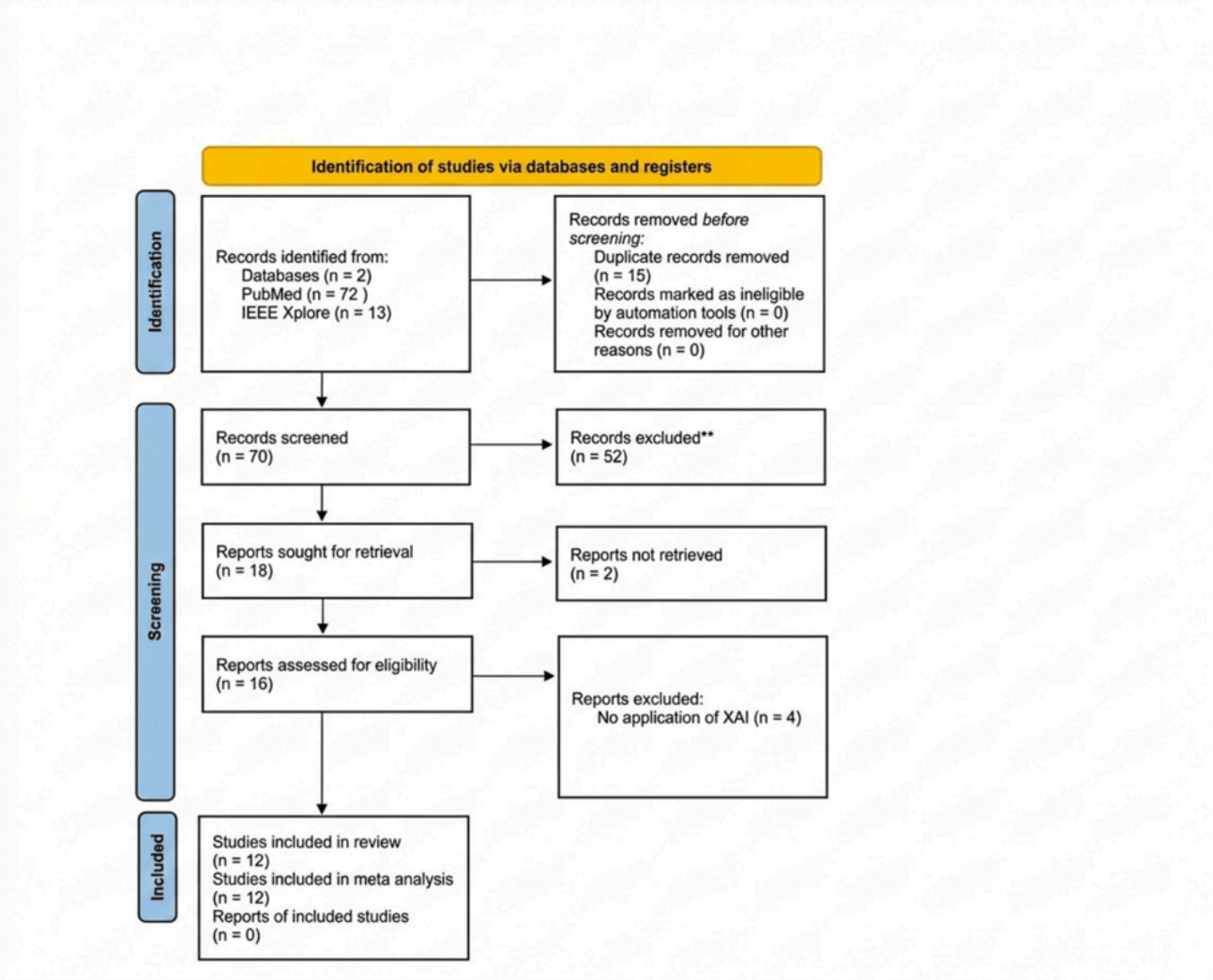

FIGURE 1: PRISMA flow diagram for systematic reviews.

XAI, explainable artificial intelligence.

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Risk of bias assessment

The author, as the sole reviewer, appraised the risk of bias on each included study by conducting an independent risk of bias assessment of the overall methodological quality, transparency of data handling, and clarity of reporting in terms of model development and results. Special focus was put on the sufficiency of the size of the dataset, the validity of the AI and XAI approaches employed, the existence or lack of external validation, and the extent to which studies addressed the possibility of confounding factors. Articles that had low methodological descriptions, no validation, or selective reporting were found to hold more bias. The risk analyses were implemented to steer the interpretation of results and to point out any shortcomings in the quality of evidence of the included studies.

Outcome

The table below (Table *1*) gives an extensive review of recent studies that use XAI methods in glioblastoma (GBM) prognosis and the optimization of its treatment. It systematically presents the main findings of 12 chosen studies, describing the ML/DL models that were used, the datasets they evaluated, the XAI methods that they deployed, and their resulting performance (AUC and accuracy). The table outlines important prognostic characteristics detected using the tools of interpretability (e.g., SHAP, LIME), molecular markers (IHD1 mutation), imaging radiomics, and clinical variables. This structured review can be used to compare the performance of models, interpretability methods and their practical importance in the development of personalized care of GBM.

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S/N	Study (First author, year)	Sample size & Data type	ML/DL model	XAI method	Key findings	AUC	Accuracy
1	**Rajput et al., 2023**	**369 MRI samples (236 train, 125 val, 29 with metadata). T1, T2, FLAIR + clinical data**	**3D U-Net + Random Forest Regressor**	**SHAP, PDP, Permutation Importance**	**29 critical features (age, tumor location, radiomics). Age >50 sharply ↓ survival. 33% improvement over BraTS-2020**	**N/A**	**0.552**
2	Raptis et al., 2024	122 patients (35–70 yrs), PET/CT + radiographic images, multi-modal radiomics + clinical	XGBoost, LightGBM, CatBoost, DNN	SHAP, LIME	DNN best (Multi-Modal AUC 0.90). Key radiomics: Surface Area, Contrast	DNN: 0.90	—
3	Palkar et al., 2024	889 glioma patients, Clinical & Mutation Dataset (UCI)	Multiple (XGBoost, CatBoost, LightGBM, ANN, CNN, etc.)	SHAP, LIME, ELI5, QLattice	XGBoost highest AUC (0.92). Top features: IDH1, age, ATRX, PTEN, EGFR, TP53	XGBoost: 0.92	XGBoost: 0.88
4	Rikan et al., 2024	19,564 classification + 28,573 regression (post-preprocessing)	XGBoost, AdaBoost, DT, KNN, RF, Feed-Forward DNN	SHAP	DNN highest accuracy (~90%). Most influential: Age at diagnosis, chemotherapy, radiation	DNN: 0.85	DNN: 0.90
5	Alahakoon et al., 2024	76 GBM patients, TCGA-TCIA MRI (~700 radiomic features)	Random Forest	SHAP	62.5% validation accuracy. Key features: HISTO_ED_T1_Bin2, TEXTURE_NG	N/A	0.625

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					TDM_ED_FLAIR_Strength		
6	Sobhan et al., 2025	347 GBM samples (CNV, mRNA, DNA methylation + pathways)	PathX-CNN	SHAP, CoxPH	AUC 0.9845. Key pathways: MAPK, Calcium, JAK-STAT. PPP2R1B poor prognosis; PRKACB & MAPK3 protective	0.9845	0.955
7	Teng et al., 2024	20,064 patients (SEER database)	CatBoost, RSF+GBM	SHAP, Feature Importance	Top 3-year predictors: surgery type, AJCC stage, M stage, tumor size, chemotherapy, age, grade	CatBoost: 0.932	CatBoost: 0.839
8	Yan et al., 2021	357 patients with gliomas (Grade II–IV), multiparametric MRI	Bayesian-regularization NN (BRNN)	LASSO, Heatmap Visualization	Predicted IDH (0.884), 1p/19q (0.815), TERT (0.669)	IDH: 0.884, 1p/19q: 0.815	IDH: 82%
9	Onciul et al., 2025	135 GBM patients	XGBoost, RF, SVM, ANN, Extra Trees, KNN	SHAP, LIME	XGBoost best (AUC 0.90, Acc 0.78). Key: KPS, MGMT, radiotherapy, age	XGBoost: 0.90	XGBoost: 0.78
10	Sadeghinasab et al., 2024	77 GBM patients (24 responders, 53 non-responders), post-surgery MRI	Multiple (Naïve Bayes, SVM, XGBoost, RF, etc.)	Feature Importance (Sequential)	Naïve Bayes best (AUC 0.86). Key radiomics: elongation, energy	NB: 0.86	NB: 0.81

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11	Bae et al., 2020	166 training + 82 validation (GBM vs metastases), CE & T2 MRI	DNN, AdaBoost, Linear SVM, LDA	Feature Importance	DNN outperformed traditional ML. Key features from T2WI median & 10th percentile	DNN: 0.956	DNN: 0.89
12	Bae et al., 2023	1,622 liver cancer patients, 46 features	RF, ET, AdaBoost, GBM, XGBoost, LightGBM, Stacking	LIME	Stacking ensemble best (93.5% accuracy). Top features: hypertension, Child-Pugh, M factor	0.9826	0.935

TABLE 1: Review of selected studies.

ML/DL, machine learning/deep learning; XAI, explainable artificial intelligence; AUC, area under the curve; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; SHAP, Shapley additive exPlanation; PDP, partial dependence plot; PET/CT, positron emission tomography/computed tomography; DNN, deep neural network; LIME, local interpretable model-agonistic explanations; ANN, artificial neural network; RF, Random Forest; KNN, k-nearest neighbor; DT, digital twin; GBM, glioblastoma multiforme; CNV, copy number variation; TCGA-TCIA, The Cancer Genome Atlas-The Cancer Imaging Archive; MAPK, mitogen-activated protein kinase; JAK, Janus kinase; CNN, convolutional neural network; SEER, Surveillance, Epidemiology, and End Results program; RSF, Random Survival Forest; SVM, support vector machine; IDH, intradialytic hypotension; ML, machine learning; LDA, linear discriminant analysis; NB, Naïve Bayes.

Table *2* presents the extracted data for meta-analysis, summarizing the best-performing models and their corresponding AUC and accuracy values across the included studies.

Year	First author	Best model	AUC	Accuracy
2020	**Bae**	**DNN**	**0.956**	**0.89**
2021	Yan	Bayesian-regularization NN	0.884	0.82
2023	Rajput	Random Forest Regressor	N/A	0.552
2023	Bae (LIME)	Stacking Ensemble	0.9826	0.935
2024	Raptis*	DNN	0.9	—
2024	Palkar	XGBoost	0.92	0.88
2024	Rikan	DNN	0.85	0.9
2024	Alahakoon	Random Forest	N/A	0.625
2024	Teng	CatBoost	0.932	0.839
2025	Sobhan	PathX-CNN	0.9845	0.955
2025	Onciul	XGBoost	0.9	0.78
2025	Sadeghinasab	Naïve Bayes	0.86	0.81

TABLE 2: Data extracted for meta-analysis.

AUC, area under the curve; CNN, convolutional neural networks; LIME, local interpretable model-agnostic explanations; DNN, deep neural network.

Findings

This systematic review summarizes recent developments in XAI used to personalize prognosis and treatment optimization in glioblastoma and other brain tumors. In multiple datasets across MRI and positron emission tomography (PET)/computed tomography (CT) imaging, genomics, and clinical records, different ML and DL models, such as Random Forests, XGBoost, CNNs, and ensemble methods, were used, and popular XAI methods, including SHAP, LIME, and attention mechanisms, were applied to make the models more interpretable. The analyzed studies showed that the implementation of explainability not only contributed to the transparency of the developed models but also allowed determining essential prognostic factors, including age, tumor site, molecular mutations (e.g., IDH1, MGMT), and radiomic features related to survival and response to treatment. The significant performance measures, such as the AUC as high as 0.98 and the accuracy of the models above 85% point to the possible clinical applicability of these models. The results, however, also show that model robustness and stability of interpretation can vary between modalities and algorithms. Altogether, the data prove the increasing importance of XAI in helping clinicians to better comprehend the AI-generated predictions, thereby developing trust and contributing to personalized decision-making in the management of GBM.

Table 3 presents the extracted AUC scores for meta-analysis, showing the distribution of discriminatory performance across the reviewed models (see Figure 2 for graphical representation).

Year	Best model	AUC
2024	DNN	0.9
2024	XGBoost	0.92
2024	DNN	0.85
2025	PathX-CNN	0.9845
2024	CatBoost	0.932
2021	Bayesian-regularization NN	0.884
2025	XGBoost	0.9
2025	Naïve Bayes	0.86
2020	DNN	0.956
2023	Stacking Ensemble	0.9826

TABLE 3: Extracted AUC scores for meta-analysis.

AUC, area under the curve; CNN, convolutional neural network; DNN, deep neural network.

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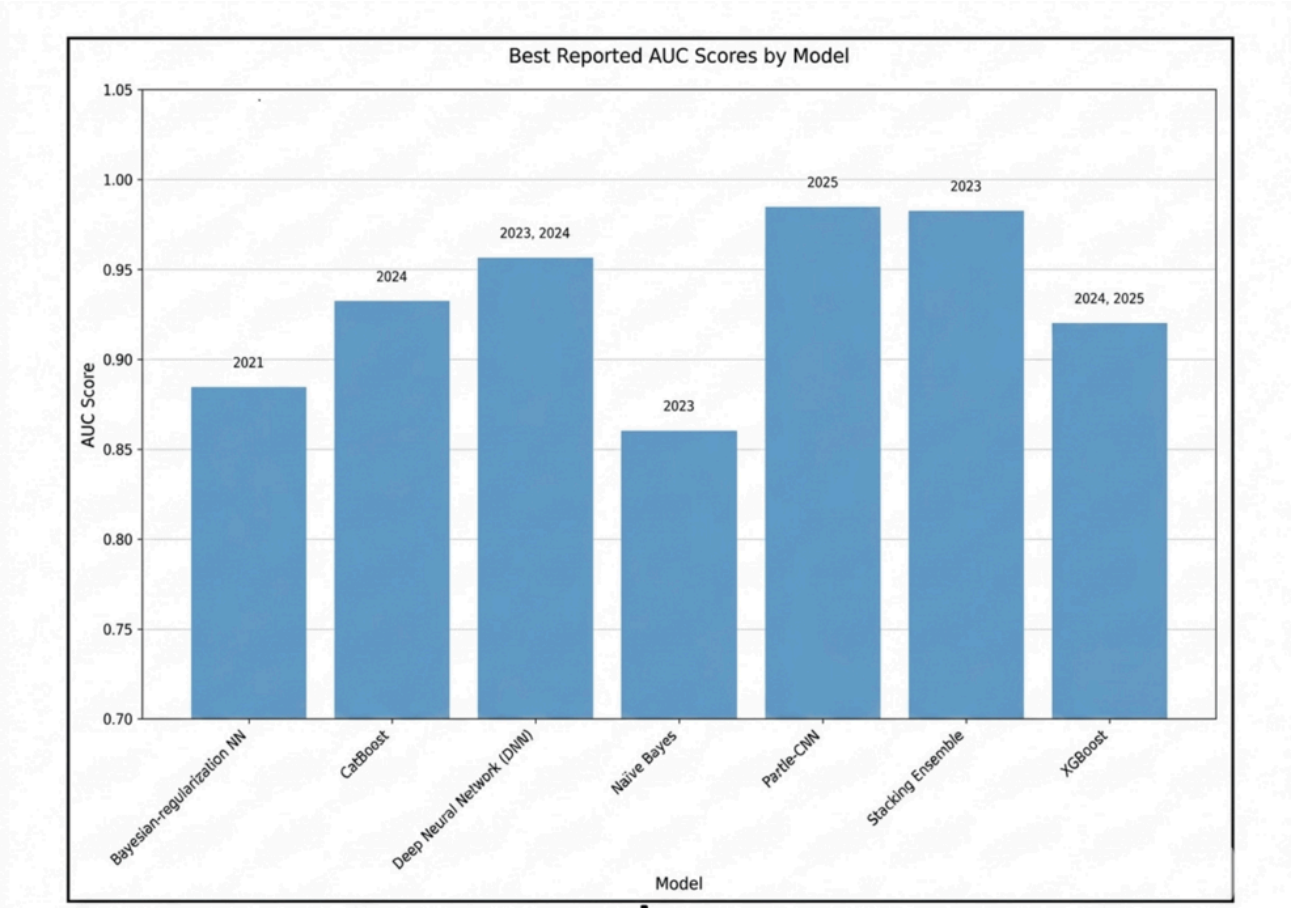

FIGURE 2: Maximum AUC scores of reviewed articles.

AUC, area under the curve; CNN, convolutional neural network.

Table *4* presents the extracted accuracy scores for meta-analysis, demonstrating the classification performance across studies (see Figure *3* for graphical representation).

Year	Best model	Accuracy
2023	Random Forest Regressor	0.552
2024	XGBoost	0.88
2024	DNN	0.9
2024	Random Forest	0.625
2025	PathX-CNN	0.955
2024	CatBoost	0.839
2021	Bayesian-regularization NN	0.82
2025	XGBoost	0.78
2025	Naïve Bayes	0.81
2020	DNN	0.89
2023	Stacking Ensemble	0.935

TABLE 4: Extracted accuracy scores for meta-analysis.

DNN, deep neural network; CNN, convolutional neural network.

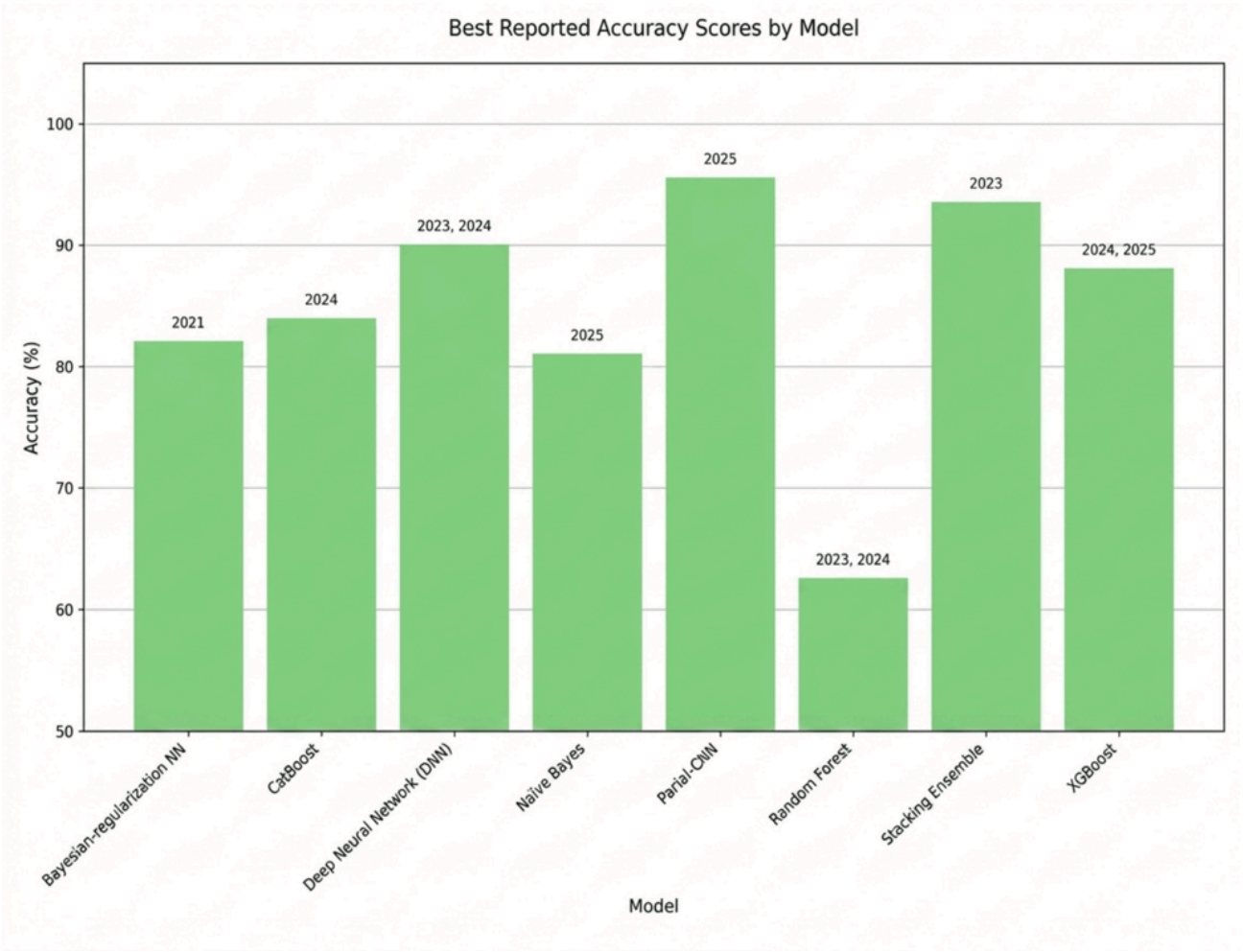

FIGURE 3: Maximum accuracy (%) of reviewed articles.

CNN, convolutional neural network.

Meta-analysis report on selected studies

In this systematic review and meta-analysis on XAI on Personalized Prognosis and Treatment Optimization in GBM, the predictive performance of the studied papers published from 2020 to 2025 was synthesized and summarized. Two key evaluation measures were highlighted, namely, the Area Under the Receiver Operating Characteristic Curve (AUC-ROC) and classification accuracy, as they are most commonly reported metrics relating to the activity of diagnostic and prognostic models in the literature reviewed.

Figure *2* presents the maximum AUC scores achieved by the best-performing models across the reviewed studies, highlighting the superior discriminatory performance of PathX-CNN and stacking ensemble approaches.

Analysis of AUC scores

The data analysis of the AUC scores calculated in the examined studies demonstrates that the degree of predictive performance of the different ML and DL models used in the context of GBM prognosis and treatment improvement tends to be high in general. The average AUC of the considered models is 0.931, which designates high discriminatory power. The AUC distribution is tightly adherent with a median of 0.932, indicating no high degrees of skewness. The PathX-CNN model obtained the highest AUC of 0.9845, showing better accuracy of survival prediction in GBM patients. On the other hand, the Naive Bayes model had the lowest AUC of 0.860, which, although also suggests a reasonable predictive power,

shows differences among models in terms of performance. These findings indicate that specialized and more advanced models, including CNNs and ensembles, might perform better than most types of simple classifiers in this field. The date of publication (2020-2025) also highlights the shifting breakthroughs in the architectures and methods of explainability, showing how far XAI methods have come towards GBM prognosis.

Analysis of accuracy (%) score

The accuracy score analysis of the studies under consideration provides an overall sense of high classification measures of predicting the outcomes of GBM and optimally treating it based on different ML models. The average accuracy of 84.5 and median accuracy of 85.9 show that, overall, there is a very strong predictive ability with relatively steady results across the different types of models. PathX-CNN gave the highest value of accuracy of 95.5% indicating that it performed best in assigning accurate outcomes to patients. Conversely, it was reported that a Random Forest model achieved the lowest accuracy of 62.5%, indicating differences in the effectiveness of models based on the algorithm and characteristics of various datasets. Based on these results, it can be noted that most of the advanced models, particularly DL and ensemble models, are likely to offer more accurate estimates in this field, whereas conventional models might provide more limited outcomes. The results of accuracy scores are also indicative of the continual development of models and validation when it comes to the application of explainable AI to the treatment of GBM over studies between 2020 and 2025.

Comparative analysis of AUC and accuracy scores

The systematic review reveals that there is substantial heterogeneity in the AUC and accuracy measures of various ML and DL models that were used in the area of GBM prognosis and optimizing treatment. In general, the values of AUC showed moderate to very high tendencies, with the best performing models being PathX-CNN and stacking ensembles that exceeded 0.98, which represents the splendid discriminatory power. The same positive performance was consistent in the accuracy scores, with the highest accuracies exceeding 90%, in the case of the PathX-CNN and stacking ensemble techniques. Although AUC offers a threshold-free estimate of model discrimination, accuracy estimates general rates of correct classification, whereas their mixed study highlights the robustness of complex, explainable AI methods in this area. This discrepancy in performance highlights the relevance of the choice of models, data heterogeneity, and validation methods. Future study directions should include standardizing evaluation protocols, increasing multi-institutional/longitudinal data collection, and incorporating multi-omics data to enhance generalizability. In addition, it will be necessary to develop explainability techniques that are specific to clinical decision support to increase trust, transparency, and clinical use of AI-based prognostic technologies in GBM management.

Figure *3* displays the maximum accuracy values reported across the included studies, demonstrating the classification performance of different ML and DL models.

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Challenges

Challenge/Limitation	Studies affected	Description	Mitigation strategies
Small sample size	**[26, 30, 33, 36]**	**Sample sizes ranging from 77 to 347 GBM patients**	**Multi-institutional data pooling; federated learning**
Retrospective design	[26–38] (majority)	All reviewed studies used retrospective designs	Prospective clinical trials with pre-defined endpoints
Class imbalance	[30, 32, 36]	Disproportionate short-term vs. long-term survivors	SMOTE-ENN, oversampling, cost-sensitive learning
Lack of external validation	[26, 28, 29, 31, 33]	Models validated only on internal/single-institution data	External validation on independent multi-center cohorts
Heterogeneous XAI methods	[26–38]	SHAP, LIME, attention, feature importance used inconsistently	Standardized XAI evaluation frameworks (e.g., causability scores)
Single-modal data	[27, 28, 31]	Reliance on imaging OR genomics alone	Multi-modal integration (radiomics + genomics + clinical)
Missing ground truth/labels	[26, 31]	Incomplete survival metadata	Standardized follow-up protocols; national registry linkage
Model overfitting	[32, 34]	High AUC may reflect overfitting to small datasets	Cross-validation, regularization, larger training sets

TABLE 5: Summary of key challenges and limitations in reviewed studies.

XAI, explainable artificial intelligence; GBM, glioblastoma multiforme; AUC, area under the curve; SMOTE, synthetic minority over-sampling technique; ENN, edited nearest neighbor; SHAP, Shapley additive exPlanation; LIME, local interpretable model-agnostic explanations.

Discussion

The review provides evidence of the increased significance of XAI in the optimized prognosis and personalized therapy of GBM. However, several critical limitations must be acknowledged. First, the majority of included studies were retrospective in design, potentially introducing selection bias. Second, the small sample sizes in several studies (ranging from 77 to 347 patients) limit the generalizability of findings to broader populations. Third, the lack of external validation in many studies raises concerns about model robustness and overfitting. Future research should prioritize prospective study designs, larger multi-institutional cohorts, and rigorous external validation to address these limitations.

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This systematic review highlights the revolutionary promise of XAI in achieving personalized GBM prognosis and treatment optimization, showing that an interpretable ML model can deliver high predictive accuracy and identify important clinically relevant biomarkers and risk factors. Through methods such as SHAP, LIME, etc., XAI helps close the gap between the complicated AI model and the clinical insights that could aid oncologists in generating better data-informed decisions. Future studies should focus on multi-modal data integration, strong external validation and standardized frameworks of XAI so that such inventions can be applied successfully to real-world clinical practice and thus provide better outcomes in GBM management.

Geographic and Resource Considerations: While this review synthesizes global evidence, the translation of XAI-GBM tools to resource-constrained settings requires consideration of infrastructure gaps, including limited access to multi-parametric MRI, genomic sequencing, and high-performance computing. Future research should evaluate the feasibility of lightweight, deployable XAI models adapted for such contexts.

Table *5* synthesizes the principal challenges encountered across the reviewed studies. The predominance of retrospective designs and small sample sizes remains the most critical barrier to clinical translation. Notably, only one study [34] incorporated external validation, underscoring the need for rigorous multi-center prospective evaluation before XAI tools can be deployed in routine clinical practice.

Conclusions

This systematic review highlights the revolutionary promise of XAI in achieving personalized glioblastoma prognosis and treatment optimization, showing that an interpretable ML model can deliver high predictive accuracy and identify important clinically relevant biomarkers and risk factors. Through such methods as SHAP, LIME, etc., XAI helps close the gap between the complicated AI model and the clinical insights that could aid oncologists in generating better data-informed decisions. Future studies should focus on multi-modal data integration, strong external validation and standardized frameworks of XAI so that such inventions can be applied successfully to real-world clinical practice and thus provide better outcomes in GBM management.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Data Availability Statements

The datasets (and/or code) supporting this study are available from the corresponding author upon reasonable request.

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