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Machine Learning Approaches for Survival Prediction in Elderly Astrocytoma Patients

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ABSTRACT

Background: Astrocytoma in the elderly population presents distinct treatment complexities associated with aging. This study used machine learning (ML) to forecast survival rates and created an online prognostic tool that operates in real-time.

Methods: The SEER database (2000–2020) was used for analysis. To identify the prognostic variables, we conducted Cox regression analysis and constructed prognostic models using five ML algorithms to predict the 5-year survival. A validation method incorporating the area under the curve (AUC) of the receiver operating characteristic (ROC) curve was used to validate the accuracy and reliability of ML models. We also performed Kaplan-Meier survival analysis.

Results: This study included 4720 patients. Survival rates varied across treatment groups, with the highest rates observed in patients who underwent combined chemoradiotherapy and surgical resection. Partial resection and no treatment were poor prognostic factors for survival, whereas surgery with chemotherapy (CTX)+ radiotherapy (RT) was a good prognostic factor for survival. Surgery + RT was a good prognostic factor for OS, whereas male sex was a good prognostic factor for CSS. ML models revealed that the most significant prognostic factor was CTX + RT. Among ML models, Random Forest Classifier (RFC) achieved the highest AUC of 0.5919.

Conclusion: Our study highlights the effective use of ML to predict survival in elderly patients with astrocytoma and reveals that extensive surgical resection combined with chemoradiotherapy improves the outcomes. We developed a novel web tool that enhances personalized treatment strategies and demonstrated the potential of ML in clinical oncology.

Keywords: Artificial Intelligence, Astrocytoma, Chemoradiotherapy, Precision Medicine, Prognosis, Survival Analysis.

Introduction

The growing elderly population, categorized by the United Nations as those over 60 years old and by the World Health Organization (WHO) as those over 65 years old, poses an expanding challenge for healthcare providers of all specialties, including neurosurgeons (1,2). This number is expected to increase by 2.9% annually by 2050 (3). Notably, certain critical studies in neuro-oncology have focused primarily on patients below the age of 70, excluding older age groups (4). Elderly patients have the highest incidence of primary brain tumors, and advanced age is considered a negative prognostic factor (5).

Astrocytoma is the most prevalent type of glioma among brain tumors. They have poor prognosis, with diverse mutations and malignancy grades (6,7). The WHO's central nervous system tumor

classification system categorizes astrocytoma into four grades, ranging from low-grade (grades I and II) to high-grade (grades III and IV) tumors, with high-grade astrocytoma peaking between 65 and 84 years of age (8–10). Higher incidence in men than in women with a sex ratio of 4:1, possibly due to the higher brain estrogen levels in women being neuroprotective (11).

The manifestations of astrocytoma include focal symptoms such as weakness, numbness, seizures, and aphasia, along with general symptoms such as headaches, vision impairments, and vomiting (7). Grade I tumors are predominantly located in the cerebellum and brainstem, grade II-IV tumors primarily affect the frontal lobe, followed by the temporal lobe (12). Brain biopsy remains the gold standard for confirming astrocytoma progression. However, circulating biomarkers such as microRNAs have shown potential in predicting disease course and treatment response. Advanced MRI assists in tumor detection and provides prognostic insights by assessing the tumor burden, vascularity, and treatment response (11).

Treatment for astrocytoma involves radiotherapy (RT), chemotherapy (CTX), and surgical resection to ease symptoms, enhance prognosis, and prevent malignant transformation (13,14). Treatment of elderly patients often lean towards less aggressive approaches due to age-related factors and higher risks (15). Therefore, refining astrocytoma treatment for elderly patients is challenging. Research focused on astrocytoma in elderly individuals remains limited, resulting in a lack of understanding of age-specific therapies. Their exclusion from clinical trials caused a gap in effective treatment of this age group (16,17).

Managing astrocytoma in elderly patients is challenging, there is a need for innovative in prognosis and therapy guidance. Machine learning (ML), a branch of artificial intelligence (AI), presents an opportunity to improve predictive accuracy by uncovering patterns that might otherwise go unnoticed (18). ML algorithms can identify prognostic factors and improve survival predictions for elderly astrocytoma patients, supporting individualized treatment decisions.

This study aimed to identify the key prognostic factors in elderly patients with astrocytoma using advanced statistical analysis and ML. Additionally, we are developing a user-friendly web-based AI tool that allows clinicians to generate real-time survival predictions, supporting treatment strategies of elderlies.

Methods

Data extraction and variables

Data were obtained from the SEER database and contains information on population, patient characteristics, tumor features, diagnosis, and healthcare data representing approximately 27.8% US population (19). Patients diagnosed with astrocytoma based on the third edition of the International Classification of Diseases for Oncology (ICD-O-3) (20) were considered for participation in the present study, the histological code for astrocytoma is 9421. Patients who met any of the mentioned exclusion criteria were excluded: age under 65 years, diagnosis not confirmed by histological examination, individuals with prior tumors or other malignancies, and those with incomplete data. A total of 4720 eligible patients were included. No imputation or case deletion were performed as the analysis was conducted on a complete SEER dataset with no missing data.

The following SEER variables were selected for the study: patient characteristics (sex, age, race, and year of diagnosis), tumor characteristics (SEER stage, primary site, and metastasis), treatment modalities, and survival information. The SEER stages were classified into three groups: localized (within an organ), regional (extension to adjacent organs or regional lymph nodes), and distant (involvement of distant organs or distant metastasis). The primary survival outcomes were overall survival (OS), calculated from diagnosis to any cause of death, and cancer-specific survival (CSS), calculated from diagnosis to death from astrocytoma.

Data Processing and Statistical Methods

Data collected from 2000-2020 were analyzed using R software (v4.2.2) with the following packages: "readxl," "tidyverse," "Hmisc," "data.table," "table1," "MatchIt," "survminer," "survival," and "broom." Chi-square analysis was used to assess categorical variables. The Kaplan-Meier (K-M) method was applied to determine survival rates, and the log-rank test was used to evaluate differences in survival curves. Cox regression models were utilized to identify independent preselected predictors of OS and CSS. Statistical significance was set at a two-tailed p-value of below 0.05. Five different machine learning models (MLM) were applied in this study to predict 5-year survival rates (21). To increase accuracy, Random Forest Classifier (RFC) was used to create several decision trees and combine their results. Gradient Boosting Classifier (GBC) to build trees sequentially, with each tree's estimation error correcting the previous one. Based on patient characteristics, Logistic Regression (LR) was used to estimate the probability of survival by using statistical approaches. K-Nearest Neighbors (KNN) to predict survival by comparing patients with the most similar patients in the dataset. Multilayer Perceptron (MLP), a type of neural network, to learn from data by adjusting the connections between layers of “neurons.” These models helped us understand the complex relationships between patient characteristics and survival outcomes, providing valuable insights into prognosis.

All the features underwent uniform standard scaling using the StandardScaler modulewithin Scikit-learn to ensure the model's robustness. Subsequently, ML models were trained on a dataset with a binary classification output predicting the target variable "5-year survival". The features included significant variables from the multivariate regression and therapeutic options. The dataset underwent a random division into an 80% portion for training and a 20% portion for testing.

The feature contribution to predicting "5-year survival" was calculated using the permutation importance method, a technique used to measure the importance of a predictive model. Receiver operating characteristic (ROC) curves and areas under the curve (AUC) scores were used to evaluate the model's discriminatory power. The roc_curve function from the sklearn.metrics module computes False Positive Rate (FPR) and True Positive Rate (TPR). The predicted probabilities of the positive class were obtained using the predict-proba method for each model. AUC scores were calculated using the roc_auc_score function. A custom plotting function, plot_roc_curve, was used to visualize the ROC curves of multiple models. Additional model evaluations included a Mean Bootstrap Estimate with a 95% confidence interval, 10-fold cross-validation, and a classification report for precision, recall, and F1-score. All ML implementations were processed using the scikit-learn 0.18 package in Python.

Results

Clinicopathological characteristics of astrocytoma patients

The study population comprised 4720 patients, with 2457 (52.1%) being males. Among the patients, 64.87% were aged 65-75 years, and only 5.89% were over 85 years old. The largest racial group was white, comprising 90.4% of the cases, and 5.3% of the cases were Asian or Pacific Islander. Furthermore, most cases were localized (83.3%, n=3,933). Frontal and temporal lobes were the most common primary locations (34% and 32.2%, respectively). 51.7% of patients underwent surgery with partial resection (37.4%) and gross total resection (14.3%). The most common therapeutic option was surgery + RT + CTX (24.4%), while the least common was CTX alone at (1.4%). Among patients over 76 years old, the most frequent approach was no treatment, followed by surgery (25.2% and 21.3%, respectively). Demographic and clinical characteristics of the patients with astrocytoma are shown in **Table 1.**

Table 1. Clinicopathological characteristics of astrocytoma patients.

Category Characteristics	> 85 years (N=278)	65-75 years (N=3062)	76-85 years (N=1380)	Overall (N=4720)	p value
Sex					
Female	125 (45.0%)	1447 (47.3%)	691 (50.1%)	2263 (47.9%)	p = 0.254
Male	153 (55.0%)	1615 (52.7%)	689 (49.9%)	2457 (52.1%)	
Race					
Asian or Pacific Islander	21 (7.6%)	152 (5.0%)	76 (5.5%)	249 (5.3%)	p = 0.401
Black	15 (5.4%)	140 (4.6%)	51 (3.7%)	206 (4.4%)	
White	242 (87.1%)	2770 (90.5%)	1253 (90.8%)	4265 (90.4%)	
Year of diagnosis					
2000-2009	171 (61.5%)	1351 (44.1%)	790 (57.2%)	2312 (49.0%)	p < 0.001
2010-2020	107 (38.5%)	1711 (55.9%)	590 (42.8%)	2408 (51.0%)	
Primary site					
Cerebrum	15 (5.4%)	312 (10.2%)	144 (10.4%)	471 (10.0%)	p = 0.04
Frontal lobe	81 (29.1%)	1045 (34.1%)	477 (34.6%)	1603 (34.0%)	
Occipital lobe	11 (4.0%)	129 (4.2%)	48 (3.5%)	188 (4.0%)	
Parietal lobe	80 (28.8%)	585 (19.1%)	273 (19.8%)	938 (19.9%)	
Temporal lobe	91 (32.7%)	991 (32.4%)	438 (31.7%)	1520 (32.2%)	
Surgery type					
Gross total resection	21 (7.6%)	464 (15.2%)	189 (13.7%)	674 (14.3%)	p < 0.001
Not performed	185 (66.5%)	1367 (44.6%)	727 (52.7%)	2279 (48.3%)	
Partial resection	72 (25.9%)	1231 (40.2%)	464 (33.6%)	1767 (37.4%)	
Stage					
Distant	12 (4.3%)	25 (0.8%)	24 (1.7%)	61 (1.3%)	p < 0.001
Localized	232 (83.5%)	2546 (83.1%)	1155 (83.7%)	3933 (83.3%)	
Regional	34 (12.2%)	491 (16.0%)	201 (14.6%)	726 (15.4%)	

Cont. Table 1. Clinicopathological characteristics of astrocytoma patients.

Category Characteristics	> 85 years (N=278)	65-75 years (N=3062)	76-85 years (N=1380)	Overall (N=4720)	p value
Treatment					
CTX	6 (2.2%)	30 (1.0%)	28 (2.0%)	64 (1.4%)	p < 0.001
CTX + RT	40 (14.4%)	603 (19.7%)	152 (11.0%)	795 (16.8%)	
No treatment	96 (34.5%)	417 (13.6%)	322 (23.3%)	835 (17.7%)	
RT	43 (15.5%)	317 (10.4%)	225 (16.3%)	585 (12.4%)	
Surgery	59 (21.2%)	471 (15.4%)	295 (21.4%)	825 (17.5%)	
Surgery + CTX + RT	18 (6.5%)	926 (30.2%)	200 (14.5%)	1144 (24.2%)	
Surgery + RT	16 (5.8%)	298 (9.7%)	158 (11.4%)	472 (10.0%)	

Survival rates of astrocytoma patients

In **Figure 1**, survival rates for sex had shown significant differences in OS (p=0.001), male sex demonstrated better OS than female patients, with a 5-year OS rate of 65.5 % compared with 58.7% in females. Additionally, CSS was significantly higher among males than females, showing a significant difference (p = 0.0011), with male sex showing a 5-year OS rate of 82% and 80.6% for females.

Gross total resection resulted in 10.5% and 14% for OS and CSS, whereas partial resection was 7.54% and 9.41% as shown in **Figure 2**. Also, KM analysis showed that these treatment-based survival differences are statistically significant for both OS and CSS, notably, Surgery + CTX + RT achieved highest survival probability, outperforming single therapeutic management and no treatment. Therapeutic groups showed significant differences in OS and CSS (p < 0.001) in **Figure 3**. Survival rates for different therapeutic methods are shown in **Table 2**. Multimodal therapy combing Surgery + CTX + RT achieved highest OS rate of 10.22%, while Surgery Alone had the highest CSS rate of 12.45%. Poorest survival outcomes were observed in RT alone, achieving an OS of 2.66% and a CSS of 4.1%.

Table 2. Five-year overall survival (OS) and cancer-specific survival (CSS) rates according to therapeutic modality.

Treatment	Overall Survival Rate (%)	Cancer Specific Survival Rate (%)
CTX	6.38	7.39
CTX + RT	4.70	5.84
No Treatment	4.12	5.94
RT	2.66	4.1
Surgery	7.15	12.45
Surgery + CTX + RT	10.22	11.4
Surgery + RT	6.21	7.1

Abbreviations: CTX: (Chemotherapy); RT: (Radiotherapy); Surgery + CTX + RT: (Surgery + Chemotherapy + Radiotherapy); Surgery + RT: (Surgery + Radiotherapy).

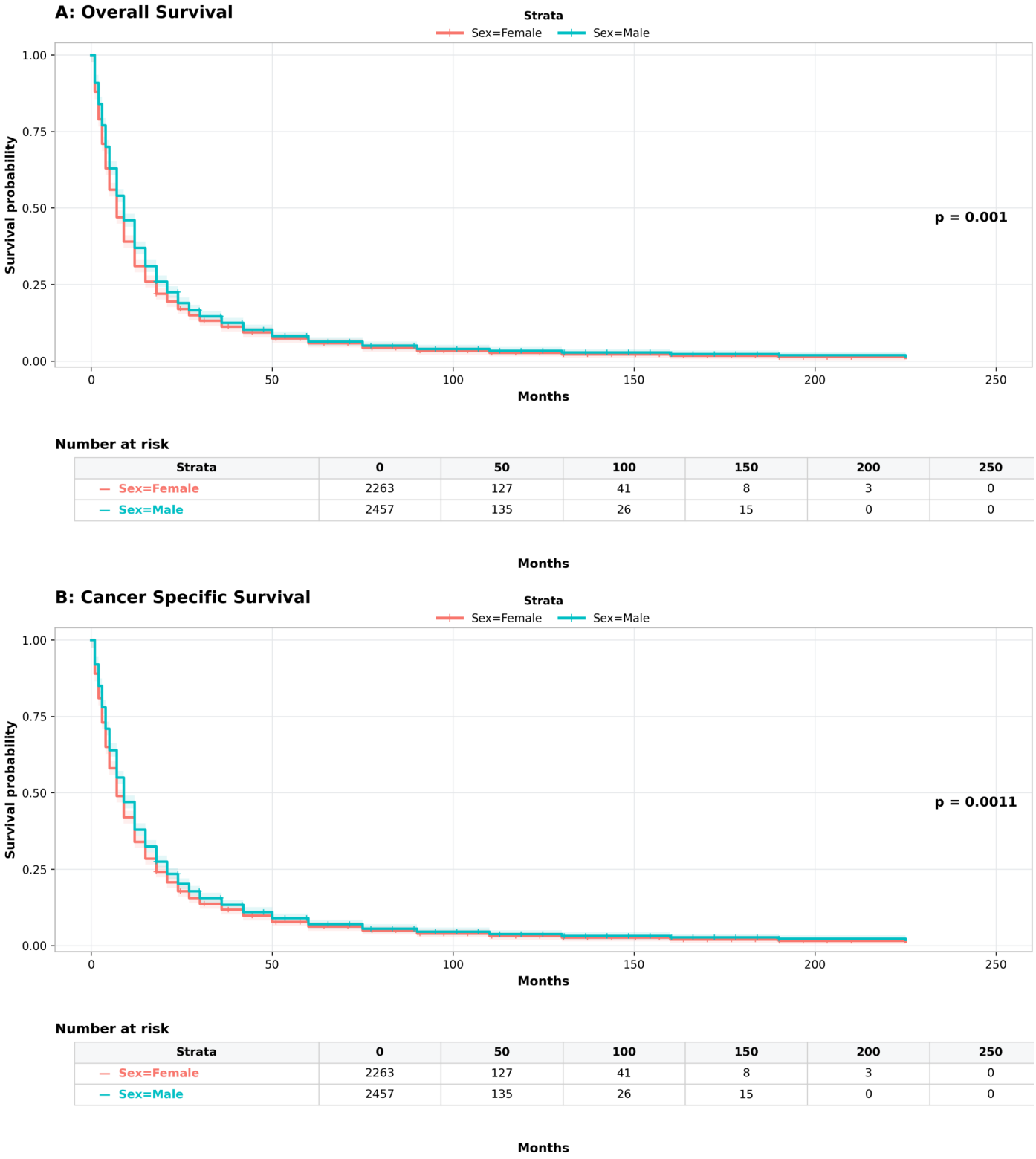


Figure 1. K-M curves for (a) OS and (b) CSS by sex.

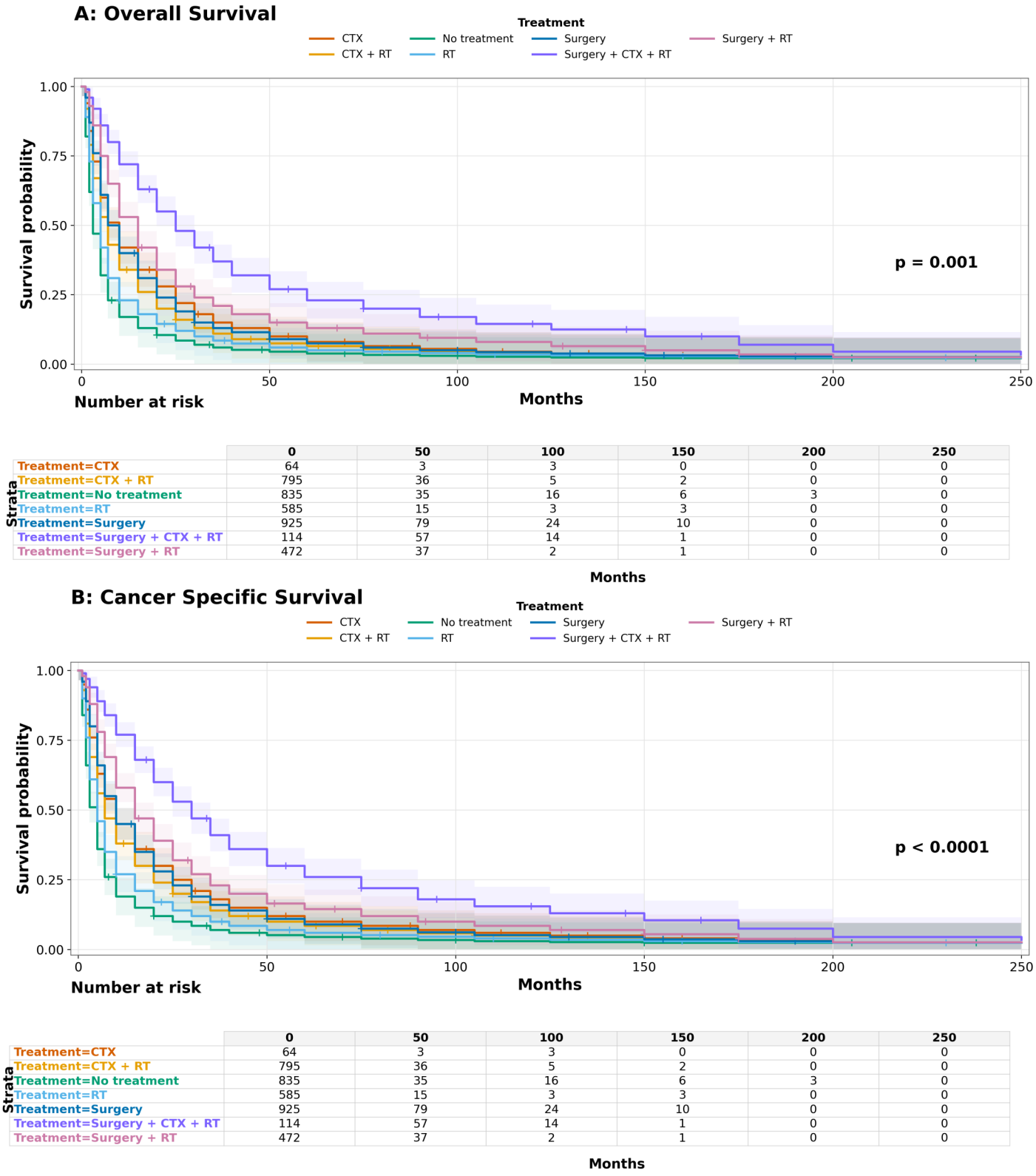
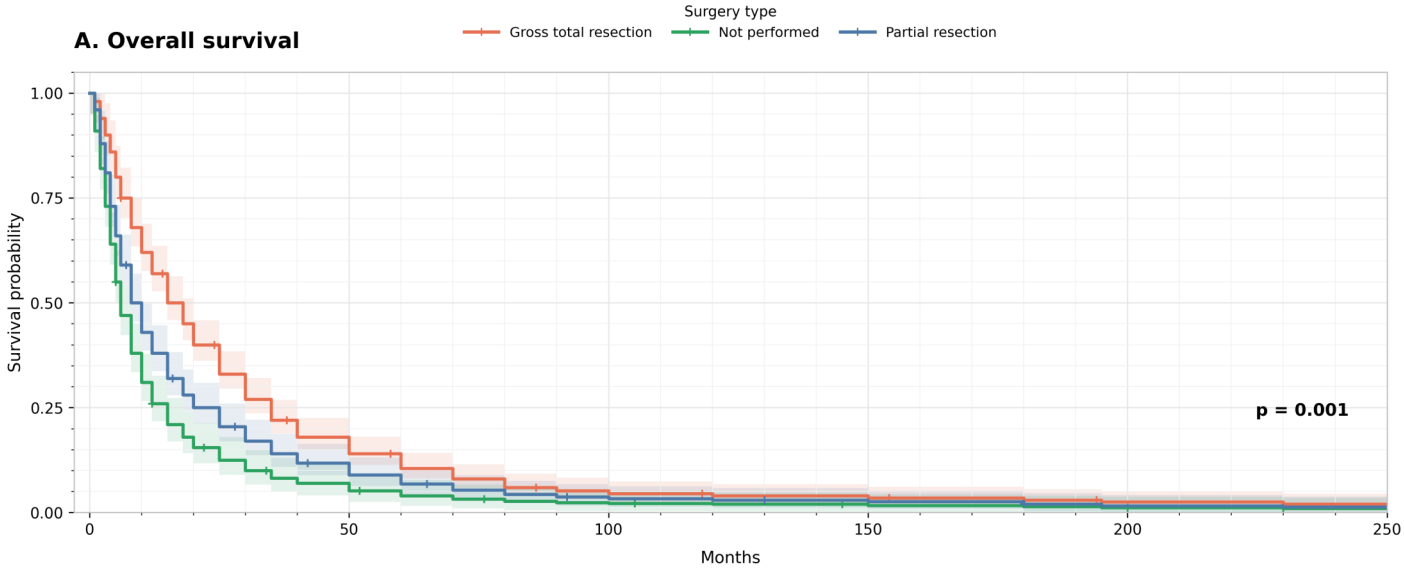
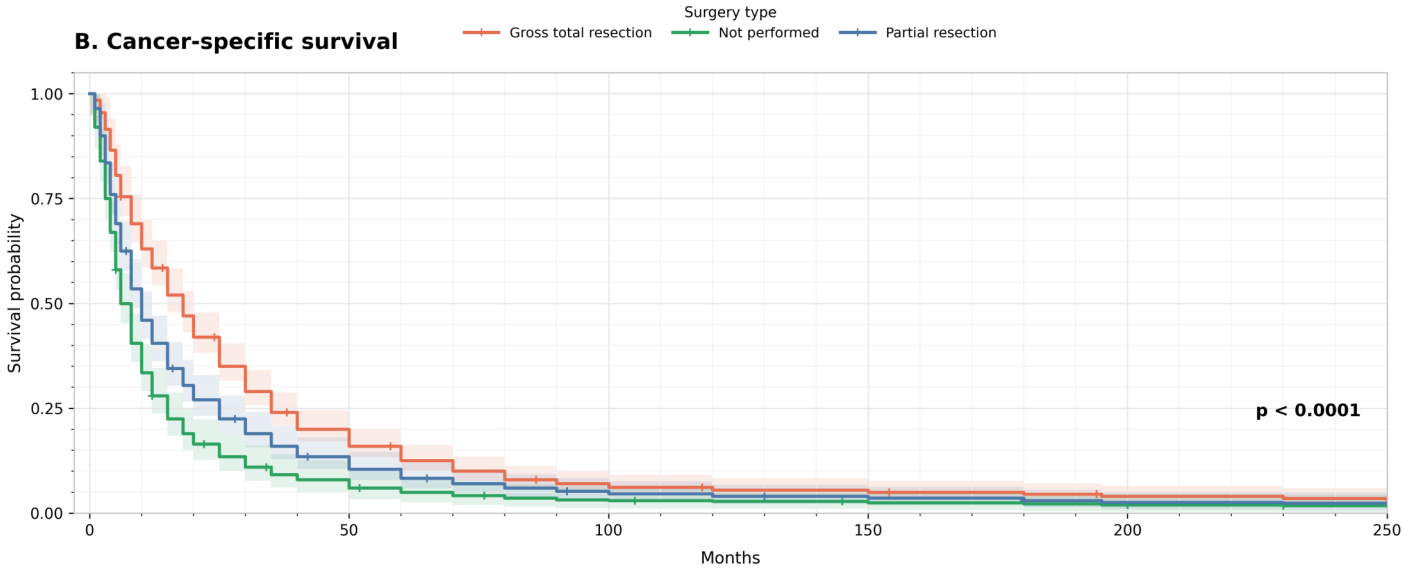


Figure 2. K-M analysis of (a) OS and (b) CSS stratified by surgery type.



Number at risk

Surgery type	0	50	100	150	200	250
Gross total resection	674	60	15	6	0	0
Not performed	2279	89	27	11	3	0
Partial resection	1767	113	25	6	0	0



Number at risk

Surgery type	0	50	100	150	200	250
Gross total resection	674	60	15	6	0	0
Not performed	2279	89	27	11	3	0
Partial resection	1767	113	25	6	0	0

Figure 3. a) K-M OS and b) CSS for treatment.

Prognostic factors in patients.

To determine the possible independent prognostic factors for OS and CSS in astrocytoma, we adopted a Univariate Cox regression model and selected only significant variables for multivariate Cox regression. Partial resection and no treatment group were poor prognostic factors for OS and CSS, whereas surgery CTX + RT was a good prognostic factor for OS and CSS. Surgery + RT was good prognostic factor for OS and male sex was good prognostic factor for CSS only **Figure 4.**

In **Supplementary-Figure1,** heatmap illustrates the correlations among treatment and patient characteristics. CT+RT correlates positively with no surgery, while no surgery correlates negatively with partial resection.

Model performances

The performance metrics for all the ML algorithms are summarized in **Supplementary-Table1.**

Figure 5A illustrates the ROC of all the MLs used. Features contributing the most to the survival are displayed in **Figure 5B**. The highest contributing factor was CTX + RT. A web-based tool was developed using Random Forest (RF) to assist clinicians, works by incorporating clinical variables to predict patient survival. Tool can be accessed at https://sakhrashwayyat.shinyapps.io/astrocytoma.

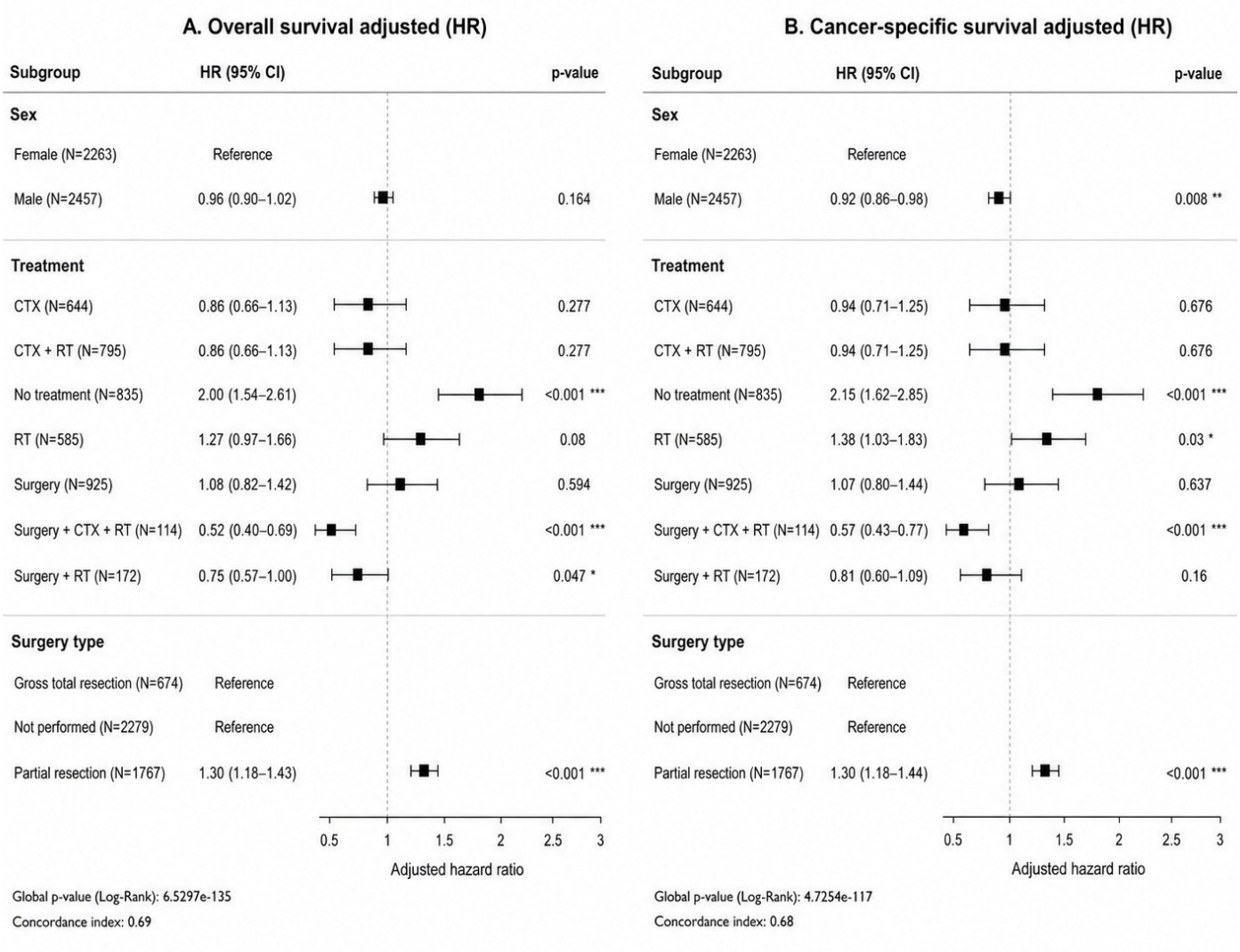


Figure 4. a) Multivariate Cox regression for OS; b) Multivariate Cox regression for CSS. *HR: (Hazard Ratio)*

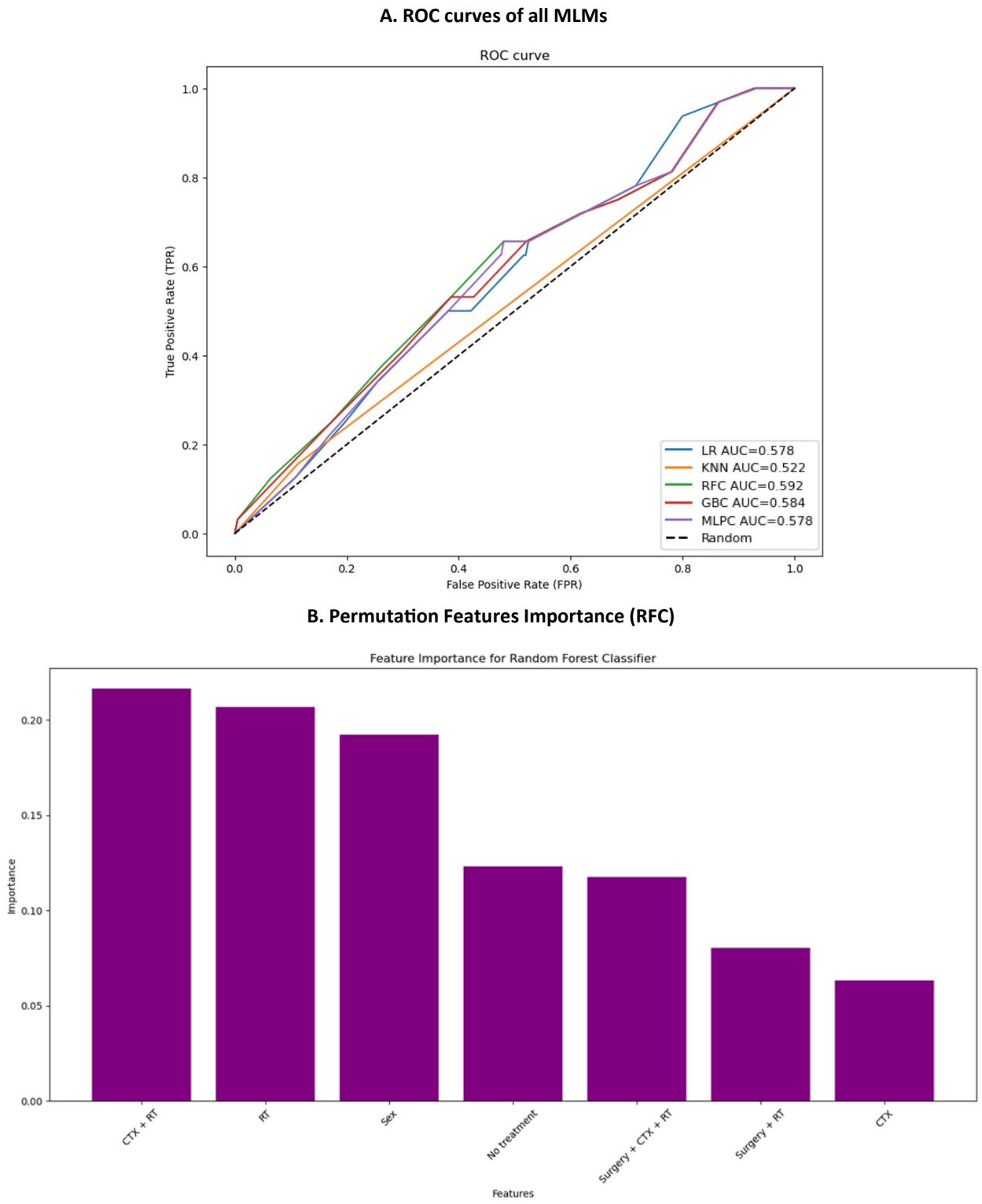


Figure 5. a) ROC curves of all MLMs; b) Permutation Features Importance (RFC).

Discussion

Limited data exists regarding astrocytomas in the elderlies, posing a clinical challenge in both diagnosis and treatment (22–24). This study identified prognostic factors that affects progression and survival.

The disease's rarity and lack of clinical trials makes it hard to define clear treatment strategies (25). A multimodal treatment approach is used, including surgery, medical, and radiation oncology (26). The disease's slow progress and patients' advanced age raise concerns about the risks of intervention. In our study, 48.3% of patients did not have surgery, and 17.7% received no treatment. Analysis showed that patients treated with medical or radiation oncology, but not surgery, had the lowest OS and CSS rates (2.66% and 4.1%). Possibly due to comorbidities that precluded surgery.

Comorbidities influence survival in patients by affecting treatment adherence, therapeutic efficacy, and overall health. A study of 604 astrocytoma patients found that 43% had comorbidities that impacted their receiving of standard therapies (27). Comorbidities contribute to disparities, lowering survival rates. Racial- and insurance-based disparities did not directly affect survival rates, income level and comorbid burden were significantly correlated with decreased survival (27).

Sex were not considered when determining treatment effectiveness (28), yet our study showed that males were more susceptible and had higher survival rates. Agreeing with Yin et al.'s (28) findings of females being less susceptible to gliomas, however suggesting that they have a better prognosis, this aligns with what Carrano et al. (29) proposed. Differences in outcomes may be due to age group, physiologic changes including immunological and hormonal changes, this could explain why sex and age differences exist (29). Our study stresses that sex is an important prognostic factor, thus, more attention should be given to gender differences. Therefore, our finding that male sex appeared favorable for CSS may reflect confounding and contradicts prior literature rather than representing a true biological effect.

Various surgical approaches were used, including total or partial tumor resection, with or without additional treatments. Multivariate analysis of 416 glioblastoma patients (grade IV astrocytoma) demonstrated that those with 98% or more of tumor volume resected had better survival rates compared to those who had less than 98% (30). Similar conclusions were drawn from other research studies (31–34), supporting our findings that partial resection adversely affects prognosis. Surgeons are advised to aim for complete tumor resections (35).

CTX+ RT for astrocytoma often results in side effects, affecting the quality of life and survival. A study of 32 high-grade glioma patients treated with CRT and temozolomide reported a median OS of 26 months and a six-month progression-free survival rate of 72.4%. Severe side effects, such as hematologic toxicity, occurred in 25-35% of patients (36), leading to treatment interruptions or dose reductions, reducing PFS and OS rates by 20-30%. Neurocognitive impairments affect up to 30% of patients and complicate therapy adherence.

Adjuvant RT is the standard of care for fit elderly patients (37). Keime-Guibert et al. demonstrated that elderly glioblastoma patients with good Karnofsky Performance Status (KPS) scores (> 60) had increased median survival compared to those receiving only supportive care (38). However, our study revealed that patients who underwent surgery alone had higher survival rates than those who received post-surgical RT. This could suggest that surgery alone may be associated with a less aggressive disease course, or it could be due to the radiation toxicity.

Our study revealed that patients who underwent surgery with CTX + RT had the highest OS rate (10.22%). Other studies yielded similar results (39). Fiorentino et al. questioned the inclusion of elderly patients with glioblastoma in CTX + RT trials and found that those with favorable prognostic factors, such as high KPS scores, experienced better survival outcomes with RT and TMZ (40). In a 2017 study including 65 glioblastoma patients, post-surgical RT was compared to RT with concomitant and adjuvant TMZ, demonstrating a significantly increased OS for the latter group, further supporting our data (41). Another study reported survival benefits in patients with a favorable prognosis (42). Both studies noted treatment toxicities but deemed them manageable. CTX + RT may be more effective than RT alone for high-grade astrocytoma elderly patients.

ML and AI hold significant potential to revolutionize clinical workflows in oncology by enhancing imaging, predictive analysis, and decision support systems. These technologies are particularly valuable in rare cancers, where limited patient numbers often constrain traditional research and clinical decision-making (43–46). AI can reduce human error and improve patient outcomes by analyzing complex datasets to reveal the hidden patterns (47).

Real-world application of AI faces challenges, including data privacy concerns, algorithmic bias, and integration difficulties. Studies indicate that up to 40% of healthcare AI applications fail to generalize across diverse patient populations because of biases in training datasets (48). Clinicians frequently lack the expertise to interpret opaque "black box" algorithms, impacting their trust and the usability of AI tools (49). The proposed integration framework emphasizes the importance of harmonizing the technical, human, and environmental domains to reduce implementation failures (50). Furthermore, high cost of implementation and the need for continuous updates further deter adoption. Ethical concerns, such as bias, transparency, and privacy, also arise with ML-based decision tools, potentially exacerbating healthcare disparities. Implementing ethical AI frameworks, including fairness audits and regulatory oversight, is crucial to ensure equitable patient care (51, 52).

Previous models for glioma prognosis that integrated clinical, radiomic, and genomic data have shown promise in terms of effectiveness. For instance, MRI-radiomics-based XGBoost models achieved an AUC of 0.72 for predicting recurrence (53). Moreover, a systematic review of 107 studies highlighted that random forests were frequently used, with radiomics-enhanced models yielding higher accuracies (54).

An AI powered web tool, that uses correlation through heatmap, was designed to predict the months of survival for individual patients by examining various prognostic factors. It can be used alongside personalized medicine strategies to enhance treatment, such as IDH mutation testing and MGMT promoter methylation analysis in astrocytoma (55, 56).

Real-world validation is essential to confirm the effectiveness of ML models in oncology research. Scoping reviews support the utility of random survival forests and neural networks, which demonstrate robust predictive capabilities with AUCs ranging from 0.6 to 0.95 (57). Explainable AI (xAI) methods enhance model transparency by identifying critical biomarkers (58), thereby building trust. Furthermore, NLP-based models that utilize electronic medical records have outperformed traditional metrics (59), underscoring the advantages of sophisticated data analysis. Future validation efforts should include diverse data sources and prospective trials to refine these models for optimal clinical applications.

This study represents the first application of ML techniques to enhance the predictive accuracy of survival rates in elderly patients with astrocytoma using a large sample size. A significant strength of this study is the development of a web-based tool that provides real-time survival predictions. This innovation facilitates practical data-driven decision-making in clinical settings, allowing healthcare professionals to tailor treatment plans more effectively based on predictive analytics. However, the retrospective nature of the data could have introduced bias, and potential biases in the SEER database may have limited the accuracy and completeness of the dataset. Moreover, the findings may not be generalizable to non-SEER populations. Additionally, the lack of detailed information about RT and CTX dosages and surgical procedures limits our ability to fully understand the impact of these treatments on patient outcomes. The data also lack measures of progression-free survival, which are crucial for evaluating

treatment efficacy over time. Also, interpretation of differences in OS and CSS across treatment modalities were limited due to the lack of adjustment for baseline performance status and comorbidity burden, as SEER lacks these clinical variables, this introduces the risk of confounding. Another limitation of this study is the absence of external validation. However, our study serves as a foundational effort that can pave the way for future studies. Future studies should explore the inclusion of genomic or molecular data in ML models to further refine the survival predictions and enhance their clinical applicability. Additionally, prospective studies incorporating user testing and clinical validation of web-based tools are needed to confirm their utility and reliability in diverse clinical settings.

Conclusion

Our study underscores the complexity of treating elderly patients with astrocytomas, highlighting several critical factors that influence outcomes. Male patients demonstrated better survival rates, suggesting a potential need for sex-specific treatment approaches. Partial resection was associated with poorer prognoses, emphasizing the importance of striving for more extensive resections, where feasible. The integration of chemoradiotherapy with surgical interventions appeared to be the most effective in enhancing both OS and CSS rates. Furthermore, the development of ML models and web tools represents a significant advancement, offering real-time personalized survival predictions that can support clinical decision-making and potentially improve patient outcomes.

Ethical approval

The ethical approval and informed consent statements are not applicable for this type of research. Authorization and data were obtained through the SEER website and database, respectively.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

Conceptualization; SA. **Formal analysis;** SA, MA. **Software;** SA, MA. **Resources;** MBAH, KM, MAMK. **Writing – original draft;** MBAH, KM, NA, TAA, YA. **Visualization;** NA. **Methodology;** TAA, YA. **Writing – review & editing;** MAMK, AJ. **Supervision;** AJ.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Material

The supplemental research materials for this study are openly available on Onedrive at the following link: Sakhr Alshwayyat et al., Supplementary Material.docx

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