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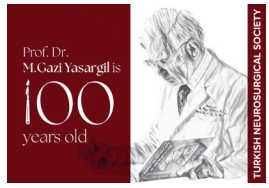

An Ensemble Learning Approach for AI-based Classification of Paraganglioma/ Pheochromocytoma, Low Grade Glioma, and Glioblastoma Tumors

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ABSTRACT

AIM: To propose a weighted vote-based ensemble classification method to classify paraganglioma/pheochromocytoma, low-grade glioma, and glioblastoma tumors—conditions that present with similar symptoms—against other central nervous system tumors using clinical and molecular data.

MATERIAL and METHODS: This study utilized clinical and molecular data from The Cancer Genome Atlas database of the United States National Cancer Institute. Initially, categorical variables were transformed into numerical values, and class distribution imbalance was addressed through oversampling. The dataset was split, with 80% used for training across 10 different classical classification algorithms and the remaining 20% reserved for testing. A weighted vote-based ensemble classification algorithm was developed using six classifiers, artificial neural networks, logistic regression, extra trees, random forest, gradient boosting, and extreme gradient boosting, selected for their high classification accuracy. Additionally, feature importance analysis identified the most critical risk factors within the dataset.

RESULTS: The proposed algorithm achieved an accuracy of 90.4% and an area under the receiver operating characteristic curve of 0.968, indicating strong classification performance.

CONCLUSION: The findings from this study suggest that the proposed method could be a valuable tool for supporting treatment planning in central nervous system tumor cases.

KEYWORDS: Central nervous system, Brain tumors, Machine learning, Ensemble classification

INTRODUCTION

Cancer is currently the second leading cause of death globally, following cardiovascular diseases (17). According to the World Cancer Report published by the World Health Organization in 2020, brain and central nervous system cancers were the 17th most common cancer type in 2018, with approximately 297,000 new cases recorded worldwide (Figure 1). The Turkey Cancer Statistics Report by the Ministry of Health indicates that brain and nervous system cancers account for about 2% of all cancer cases across age groups and genders (10). These cancers also rank as the 10th leading cause of cancer-related deaths worldwide (Figure 2) (17).

Gliomas are a type of central nervous system tumor categorized by the World Health Organization into four grades based on histopathological features. Grade 1 gliomas are benign, grow slowly, and have limited spread, while grade 4 gliomas are aggressive and possess metastatic characteristics (15). Gliomas represent nearly 80% of all primary malignant brain tumors, with glioblastoma, a grade 4 tumor, comprising more than 60% of all brain tumors in adults (18).

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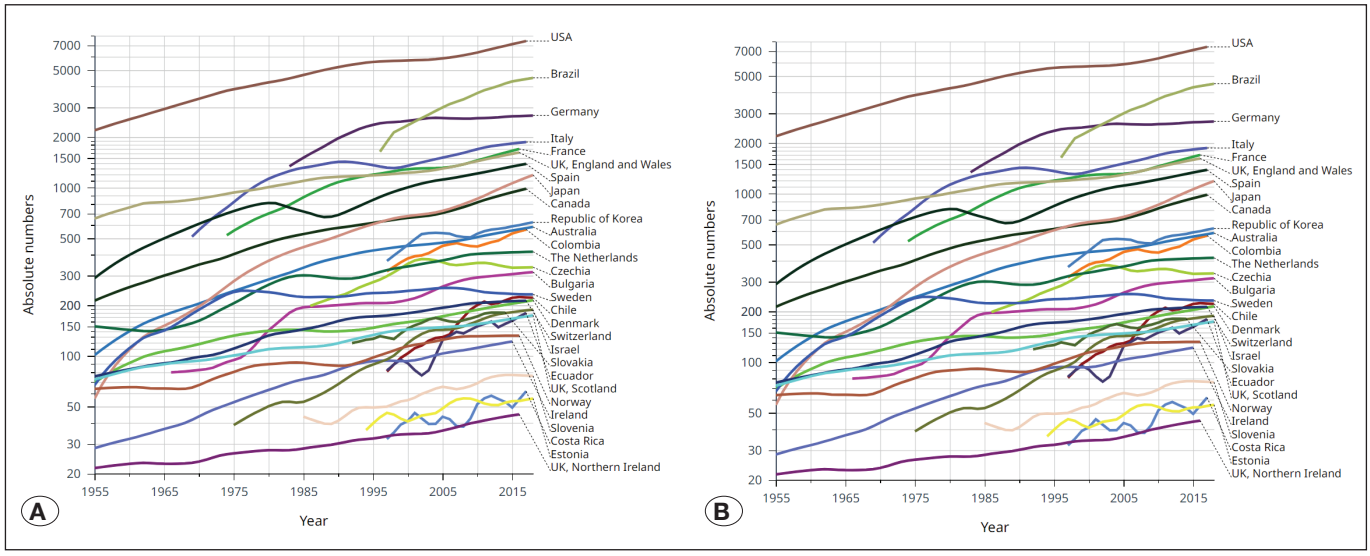

Figure 1: Incidence of brain and other central nervous system cancers **A)** among women **B)** among men (Source: GLOBOCAN)

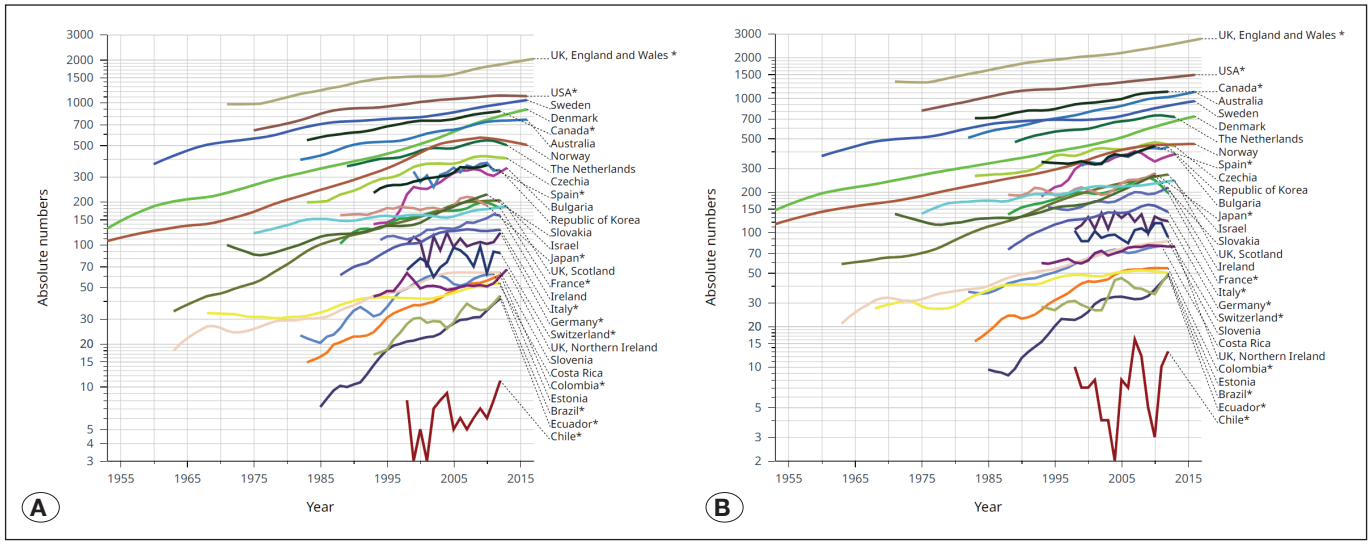

Figure 2: Mortality numbers of brain and other central nervous system cancers **A)** among women **B)** among men (Source: GLOBOCAN).

Paragangliomas are rare neuroendocrine tumors of the nervous system, originating from the adrenal gland or ganglia in various parts of the body. These tumors show significant genetic diversity, with up to 40% of cases linked to germline mutations (16). The molecular pathomechanism of paraganglial tumors remains largely unknown. Pathways, such as activation of the Hypoxia Inducible Factor 1a (HIF1a) related to neoangiogenesis and Ras oncogene activation, are implicated. In head and neck paragangliomas, pseudohypoxia resulting in succinate accumulation due to mitochondrial dysfunction may be a primary mechanism (12). Since the World Health Organization's 4th edition of central nervous system cancer classifications, paragangliomas are no longer classified as benign or malignant, as any lesion may carry metastatic potential, with no definitive features predicting this behavior. Moreover, some tumors are lethal without metastasis due to local invasion involving critical structures (14).

Both gliomas and paragangliomas present with similar symptoms, such as headache, sweating, and tachycardia (10,19). Recently, molecular changes have become increasingly significant in classifying central nervous system tumors; however, clinical features such as age and gender also contribute to tumor grading. Despite this, publicly available datasets often lack sufficient information linking molecular and clinical features that could enhance the value of patient care. Selecting optimal molecular and clinical markers not only reduces healthcare costs and treatment expenses but also helps address growing health inequalities in access to testing. Moreover, this approach improves tumor grading accuracy, allowing for the identification of relevant molecular features for future analysis (18).

A range of treatment options exists for brain and central nervous system tumors. Beyond surgical intervention, treatments

include general radiation therapy, local radiosurgery, and chemotherapy, applied either alone or in combination. Immunotherapy has also emerged as a promising option. However, recent molecular and genetic studies have revealed that glioblastoma (GBM), the most aggressive brain tumor, includes subtypes with unique molecular diagnostic markers that significantly affect patient survival (19). It is now also recognized that paragangliomas, like high-grade tumors, can recur and metastasize (14). Given the similarity in symptoms and affected areas, along with their associated risks, it is essential to distinguish these tumors accurately. The World Health Organization has recently acknowledged that paragangliomas can exhibit aggressive and metastatic behavior, prompting their removal from the category of low-grade central nervous system tumors. Paragangliomas are primarily treated surgically and generally have a higher patient survival rate than gliomas. Thus, determining the tumor type and stage is crucial for effective treatment planning. In this context, further studies on the classification of diverse central nervous system tumors are essential to enhance understanding and improve treatment outcomes.

This study presents a classification method supporting the hypothesis that distinct molecular and clinical data can effectively distinguish paragangliomas from low- and high-grade gliomas. Clinical and mutational datasets from the paraganglioma/pheochromocytoma, low-grade glioma, and glioblastoma projects (TCGA-PGPC, TCGA-LGG, and TCGA-GBM) in The Cancer Genome Atlas (TCGA) database, provided by the US National Cancer Institute, were utilized. To achieve optimal results, the performance of classical machine-learning methods was tested individually, followed by experiments using various combinations of supervised classification models with a weighted voting approach. According to our research, this study is the first classification study that leverages molecular and clinical data to differentiate between paragangliomas and gliomas.

MATERIAL and METHODS

Dataset

This study utilized clinical and molecular data from PGPC, LGG, and GBM, central nervous system tumors with similar symptoms, available in TCGA database by the United States National Cancer Institute (22). The dataset consisted of a total of 1,197 samples across three classes: 0 (PGPC), 1 (LGG), and 2 (GBM). These included 358 samples in the PGPC class, 487 in the LGG class, and 352 in the GBM class.

Each sample was defined by 25 attributes (Table I). Three were clinical attributes, gender, age at diagnosis, and race, while the remaining 22 were molecular attributes related to the tumors. Clinical attributes were transformed into numerical values, and molecular attributes were assigned based on the mutational status of specific genes known to undergo significant mutations in association with these tumors. Each gene was assigned a value of 1 if a mutation was present and 0 if absent.

During preprocessing, records with values such as “not_reported” and “--” in clinical attributes were removed, as they were not expected to contribute to the classification. However, to avoid loss of valuable data in the smaller PGPC class, samples where “Race” was marked as “not_reported” were retained. All samples in the PGPC class, which initially contained fewer records (179) compared to the other classes, were duplicated to reach a total of 358 samples, balancing the dataset.

Proposed Method

Central nervous system tumors account for approximately 1.6% of all human tumors and are among the most complex cancers. Despite their anatomical similarities, these tumors exhibit distinct morphology, etiology, site of origin, molecular biology, and clinical progression (11). Numerous significant prediction and classification studies have been published regarding the grading of nervous system tumors. In this study, we propose a weighted vote-based ensemble classification algorithm for tumor prediction, utilizing clinical and molecular data from PGPC, LGG, and GBM from TCGA database.

Ensemble learning algorithms are among the most effective machine-learning methods in predictive analytics. Ensemble classifiers combine multiple machine-learning algorithms, known as base learners, to create high-accuracy models by integrating several individual classifiers (1).

The proposed weighted vote-based ensemble classification algorithm consists of three stages. In the first stage, the TCGA clinical and molecular dataset is preprocessed. Records with missing data in more than one attribute are eliminated. To address the unbalanced distribution caused by the PGPC class, which contains fewer records (179) than the other classes, all samples belonging to the PGPC class were duplicated, resulting in a total of 358 samples. The data transformations are as follows:

- Age at diagnosis, initially represented as integer values, was converted to floating-point numbers by dividing the total number of days lived by 365.
- Categorical values of the race variable were transformed into integer values ranging from 0 to 3 (White → 0, Black or African American → 1, Asian → 2, American Indian or Alaska Native → 3).
- “Male” values in the gender variable were replaced with 0, while “Female” values were replaced with 1.
- The “Grade” variable, which represents the class label, was assigned the following integer values: 0 for PGPC, 1 for LGG, and 2 for GBM.

These clinical data were then merged with gene mutation status information from the mutation database. Genes with mutations, excluding silent mutations, RNA mutations, and non-coding region mutations, were assigned a value of 1, while those without such mutations were assigned a value of 0. At this stage, driver genes known to be most frequently mutated in the relevant central nervous system tumor types, along with other genes believed to have a differential effect, were selected as attributes.

Table I: Clinical and Molecular Attributes and Value Ranges of TCGA Central Nervous System Tumors

#	Attribute Name	Type	Value Range (or Values)
1	Grade	Class	0 (PCPG) – 1 (LGG) – 2 (GBM)
2	Gender	Clinical	0 (Male) – 1 (Female)
3	Age_at_diagnosis	Clinical	14,42 – 89,29
4	Race	Clinical	0 (White) – 1 (Black or African American) – 2 (Asian) – 3 (American Indian or Alaska Native)
5	IDH1	Molecular	0 (No Mutation) – 1 (Mutation Exists)
6	TP53	Molecular	0 (No Mutation) – 1 (Mutation Exists)
7	ATRX	Molecular	0 (No Mutation) – 1 (Mutation Exists)
8	PTEN	Molecular	0 (No Mutation) – 1 (Mutation Exists)
9	EGFR	Molecular	0 (No Mutation) – 1 (Mutation Exists)
10	CIC	Molecular	0 (No Mutation) – 1 (Mutation Exists)
11	MUC16	Molecular	0 (No Mutation) – 1 (Mutation Exists)
12	PIK3CA	Molecular	0 (No Mutation) – 1 (Mutation Exists)
13	NF1	Molecular	0 (No Mutation) – 1 (Mutation Exists)
14	PIK3R1	Molecular	0 (No Mutation) – 1 (Mutation Exists)
15	FUBP1	Molecular	0 (No Mutation) – 1 (Mutation Exists)
16	RB1	Molecular	0 (No Mutation) – 1 (Mutation Exists)
17	NOTCH1	Molecular	0 (No Mutation) – 1 (Mutation Exists)
18	BCOR	Molecular	0 (No Mutation) – 1 (Mutation Exists)
19	CSMD3	Molecular	0 (No Mutation) – 1 (Mutation Exists)
20	SMARCA4	Molecular	0 (No Mutation) – 1 (Mutation Exists)
21	GRIN2A	Molecular	0 (No Mutation) – 1 (Mutation Exists)
22	IDH2	Molecular	0 (No Mutation) – 1 (Mutation Exists)
23	FAT4	Molecular	0 (No Mutation) – 1 (Mutation Exists)
24	PDGFRA	Molecular	0 (No Mutation) – 1 (Mutation Exists)
25	HRAS	Molecular	0 (No Mutation) – 1 (Mutation Exists)
26	TTN	Molecular	0 (No Mutation) – 1 (Mutation Exists)

In the second stage, classification was performed using ten different classifiers: neural network (NN), logistic regression (LR), extra trees (ET), random forest (RF), naive Bayes (NB), k-nearest neighbors (KNN), support vector machine (SVM), adaptive boosting (AB), gradient boosting (GB), and extreme gradient boosting (XGB). In the third stage, reclassification was conducted using the weighted vote-based ensemble classification algorithm, which included the six classifiers with the highest accuracy rates.

In the final stage, the accuracy and confusion matrix of the prediction results from the weighted vote-based ensemble classification algorithm were generated, and the results were compared to the performance of the individual classifiers. A flow diagram of the proposed algorithm is presented in Figure 3.

Performance Evaluation Metrics

The performance evaluation of a classification model after the training phase is based on its ability to correctly classify examples in the test set. The number of correctly and incorrectly classified instances can be summarized in a matrix known as the confusion matrix, as shown in Table II (3).

The definitions of the values in this table are as follows:

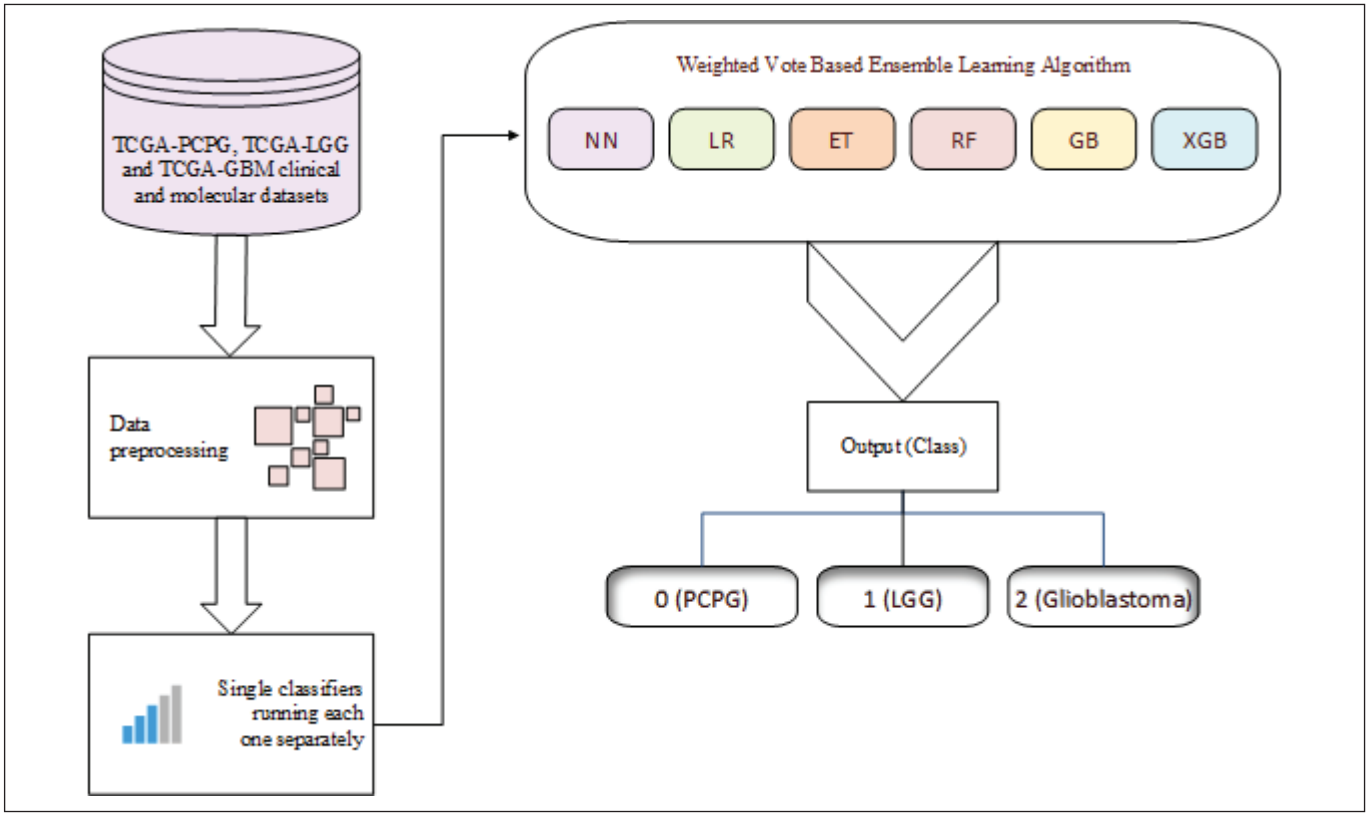

Figure 3: Flow diagram of the proposed classification algorithm.

Table II: Confusion Matrix for Binary Classification

	Predicted: 1	**Predicted: 0**
Actual: 1	TP	FN
Actual: 0	FP	TN

True Positive (TP): The number of samples that are positive (1) and classified as positive.

False Negative (FN): The number of samples that are positive (1) but classified as negative.

False Positive (FP): The number of samples that are negative (0) but classified as positive.

True Negative (TN): The number of samples that are negative (0) and classified as negative.

While the confusion matrix provides general information about the model's performance, various other performance metrics can be derived from it. Accuracy, precision, recall, and F-measure are some of these metrics. Among them, accuracy is one of the simplest and most widely used performance measures, defined as the ratio of correctly classified samples to the total number of samples in the test set. The performance measures for these four metrics are calculated using Equations (1), (2), (3), and (4).

$$\text{Accurarcy (ACC)} = \frac{TP + TN}{TP + TN + FP + FN} \quad (1)$$

$$\text{Recall} = \frac{TP}{TP + FP} \quad (2)$$

$$\text{Precision} = \frac{TP}{TP + FN} \quad (3)$$

$$\text{F - measure} = \frac{2 * Precision * Recall}{Precision + Recall} \quad (4)$$

The F-measure is a hybrid metric designed for evaluating unbalanced classes. The ROC (receiver operating characteristic) curve illustrates the relationship between the false positive rate and the true positive rate at various thresholds. To quantify the effectiveness of this curve, the area under the ROC curve (AUC) or ROC AUC score is calculated. The AUC serves as a measure of separability: the larger the area under the curve, the better the classification algorithm performs in distinguishing between classes (4).

To evaluate the performance of the proposed method alongside classical classification techniques, the performance metrics of accuracy, precision, recall, F-measure, and AUC are employed.

RESULTS

The method proposed in this study, along with the classification techniques used for comparison, was implemented in a Jupyter Notebook environment using the Python programming language on a computer equipped with a 13th Generation Intel Core i9 13900HX processor (2200 MHz), 32 GB of RAM, and a 64-bit Windows 11 Home operating system. The scikit-learn library, known for its extensive user base and comprehensive machine-learning functions, was utilized in the applications.

Figure 4 presents a bar graph illustrating the discriminative importance of the features in the dataset. This graph was generated using the "feature_importances_" function of the RF classifier. As shown in the figure, the mutation status of the IDH1 gene contributes the most to classification success, followed by age at diagnosis and the mutation statuses of the TP53, PTEN, and CIC genes. In the dataset, which comprises a total of 25 attributes, it was observed that reducing the number of attributes through selection negatively impacted classification success. Consequently, all attributes in the dataset were included in the study.

No normalization or standardization was performed on the data. The dataset was divided into training (80%) and testing (20%) subsets. After classifying the data with 10 different single classifiers, the correct classification performances were assessed. The six classifiers with the highest accuracy rates (NN, LR, ET, RF, GB, and XGB) were selected to form an ensemble-based classification structure. The performance comparisons of the proposed weighted vote-based ensemble classification algorithm and the individual classifiers are presented in Table III, while Table IV displays the confusion matrix of the proposed classification algorithm.

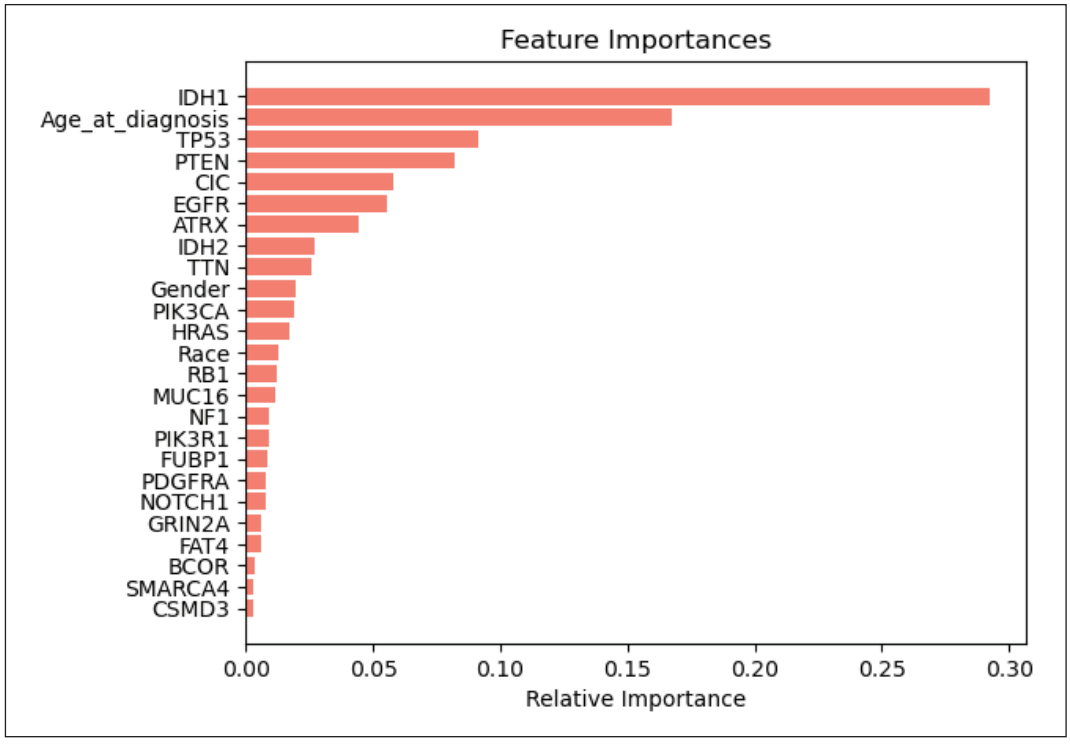

Figure 4: Bar graph showing the importance of the attributes in the dataset.

Table III: Performance Comparison of Individual Classification Algorithms and the Proposed Ensemble-Based Algorithm

	Accuracy	Precision	Recall	F-measure	AUC
Proposed Algorithm	**0.904**	**0.909**	**0.905**	**0.905**	**0.968**
NN	0.888	0.894	0.890	0.890	0.954
LR	0.888	0.894	0.890	0.890	0.956
ET	0.883	0.881	0.884	0.881	0.956
RF	0.875	0.880	0.877	0.875	0.966
GB	0.875	0.878	0.876	0.875	0.957
XGB	0.883	0.883	0.884	0.882	0.966

Table IV: Confusion Matrix of the Proposed Algorithm

	Predicted: 0 (PCPG)	Predicted: 1 (LGG)	Predicted: 2 (GBM)
Actual: 0 (PCPG)	**77**	0	0
Actual: 1 (LGG)	3	**87**	7
Actual: 2 (GBM)	9	4	**53**

Table III demonstrates that the proposed classification algorithm outperforms the individual classifiers in terms of both accuracy and other performance metrics. An examination of the confusion matrix in Table 4 reveals that the algorithm can distinguish the 0-PGPC class with 100% accuracy. However, the accuracy rate for the 2-GBM class decreases to approximately 80%. This trend is consistent across the individual classifiers, indicating that GBM exhibit more complex and heterogeneous characteristics compared to LGG and PGPC. Additionally, the confusion matrix suggests that GBM share more clinical and molecular characteristics with PGPC than with LGG. Nonetheless, the overall performance of the proposed method remains satisfactory, as indicated by the accuracy and F-measure metrics, which are crucial for medical diagnostics.

DISCUSSION

Malignant brain and nervous system tumors are prevalent worldwide and pose significant treatment challenges. Detecting and preventing these tumors at an early stage remains difficult. To aid in early diagnosis, expert systems, artificial intelligence, and machine-learning techniques are increasingly employed to assist healthcare professionals.

Recent advancements in bioinformatics and information technologies have unveiled various molecular and prognostic factors related to central nervous system cancers, enabling researchers to develop diverse classification models. Numerous techniques have been applied in the literature to classify both primary and metastatic brain tumors among various nervous system tumors. For instance, Tasci et al. proposed a hierarchical vote-based ensemble classification model using data from low- and high-grade gliomas sourced from the TCGA and Chinese Glioma Genome Atlas (CGGA) databases. Their results demonstrated accuracy rates of 87.6% and 79.7% on the TCGA and CGGA datasets, respectively (18). Joo et al. classified three tumor types—GBM, central nervous system lymphoma, and brain metastasis—using MRI images with methods such as LASSO, SVM, AdaBoost, and ensemble learning, achieving a classification accuracy of 76.3% with the ensemble learning algorithm (9). Chang et al. utilized convolutional neural networks (CNNs) to predict genetic changes in low- and high-grade gliomas from MRI images, showing that neural networks can yield successful results without necessitating feature selection in image processing. They further enhanced their results by extracting critical features using principal component analysis in the final layer (6). Sarhan's study focused on predicting tumor malignancy from MRI images, achieving an impressive overall classification success of 99.3% by training a dataset that included discriminative features extracted via the Discrete Wavelet Transform algorithm on a CNN (15). Mehrotra et al. also employed MRI images in a transfer learning approach to predict tumor malignancy, achieving 99% accuracy (13). Djirackor et al. presented a model for intraoperative classification of brain tumors, leveraging low-coverage nanopore array and DNA methylation profiles generated through machine-learning algorithms, which resulted in an accuracy of 89% (7). Bathla et al. found that machine-learning and deep-learning algorithms performed comparably in classifying metastatic brain tumors, GBM, and central nervous system lymphoma using MRI data (5). Vidyadharan et al. introduced an ensemble-based machine-learning algorithm utilizing brain images obtained through diffusion tensor imaging to classify low- and high-grade gliomas, achieving 92% sensitivity and 90% specificity (21). In the work of Al-Azwii and Nazarov, a binary classification algorithm demonstrated 96.6% accuracy by training brain image data with an ensemble deep-learning model (2). Similarly, Hossain et al. presented a transfer learning algorithm utilizing various deep-learning architectures on brain MRI images, achieving the highest accuracy rate of 96.94% (8).

A review of the literature reveals that brain tumors are predominantly classified using image data, with success rates that are generally comparable. However, this study takes a different approach by analyzing both molecular and clinical data in a hybrid manner, presenting a multi-class prediction model that includes not only brain tumors but also paragangliomas, which are another type of central nervous system tumor. The inclusion of paragangliomas is significant due to their ability to cause symptoms similar to gliomas and the recent understanding that they can be aggressive and metastatic.

In this study, we introduce a weighted vote-based ensemble classification algorithm that achieves an accuracy of 90.4% for classifying central nervous system tumors, including paragangliomas, LGG, and GBM. These tumors can be diagnosed and treated by specialists in brain and neurosurgery. The classification algorithm presented here aims to assist experts in making informed decisions in the field. The findings suggest that when machine-learning models are trained with the appropriate features, they can effectively facilitate complex, time-consuming, and risky tumor diagnosis procedures.

Despite the promising results, this study has several limitations. First, the data were sourced from a single center's database. Incorporating data from multiple centers would likely yield more accurate and representative results. Second, as the dataset exclusively consists of patients of American origin, the effectiveness of the proposed method may differ among patients of various ethnic backgrounds. Greater ethnic diversity in the data could enhance the generalizability of the findings.

In recent years, the concept has emerged that metabolic reprogramming in cancer cells is an active rather than a passive process. Oncogenes and inactive tumor suppressors directly influence the metabolism of these cells. Altered metabolism in brain and other central nervous system tumors can be utilized for both diagnosis and treatment. Blocking tumor metabolism

as a therapeutic strategy has shown significant promise in preclinical models. However, these studies present substantial challenges due to factors such as blood-brain barrier penetration, the presence of tumor stem cells, tumor heterogeneity, and variations in the microenvironment, all of which may contribute to treatment resistance and tumor recurrence. One potential approach is to block multiple metabolic pathways or to combine metabolic targets with conventional therapies for more effective treatment of these tumors (20).

CONCLUSION

In conclusion, our findings contribute to the development of similar predictive models. This study can be expanded in the future by incorporating various biomedical and molecular data and utilizing a combination of different classification techniques, which could enhance classification success. Furthermore, it can be generalized by including various brain and central nervous system tumors within the system.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

Ethical statement: Ethical approval is not applicable for this article (https://trdizin.gov.tr/wp-content/uploads/2022/04/TRDizin_etik_ilkeleri_akis_semasi.pdf).

AUTHORSHIP CONTRIBUTION

Study conception and design: SA

Data collection: SA

Analysis and interpretation of results: SA

Draft manuscript preparation: SA

Critical revision of the article: GO

Other (study supervision, fundings, materials, etc...): EG

All authors (SA, GO, EG) reviewed the results and approved the final version of the manuscript.

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