

# IARCO Research Proposal (5) - Kashfia Arisha.pdf

*by* Sanaul Haque

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## **IARCO Research Proposal**

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**Research Topic:** Integrating Molecular Markers and Clinical Factors with Treatment Adherence to Uncover Patterns of Malignant Brain Tumor Recurrence in Bangladesh : A Retrospective Cohort Study on Glioblastoma Multiforme

## **Integrating Molecular Markers and Clinical Factors with Treatment Adherence to Uncover Patterns of Malignant Brain Tumor Recurrence in Bangladesh: A Retrospective Cohort Study on Glioblastoma Multiforme**

### **Introduction:**

Malignant brain tumors are life-threatening, aggressive, and rapidly growing, capable of invading healthy brain tissue and compromising vital neurological functions [1]. This study focuses on primary brain tumors, specifically, one of the most aggressive variants, Grade IV—Glioblastoma (GBM) (according to WHO classification) [2,7]. The exact causes of GBM are largely unknown, but age, obesity [12], smoking, gender, and genetic predispositions etc may statistically put one at increased risk [3]. The standard treatment for newly diagnosed GBM is the Stupp Protocol, which includes maximal surgical resection, concurrent radiotherapy with temozolomide (TMZ), and continued adjuvant TMZ [13]. Despite this multimodal approach, recurrence (new or enlarging enhancing lesion on MRI per RANO criteria) is common due to the tumor's aggressive nature [15]. Globally, GBM incidence is estimated at 3.19–4.17 cases per 100,000 per year [3]. In Bangladesh, brain tumor incidence is around 2–3 per 100,000 per year, although there is limited data on specifically GBM. [10]. The Stupp Protocol is not accurately followed in most LMICs and Bangladesh is no different. Despite improvements in healthcare, proper implementation of treatment protocols, accurately recording and storing patient data and eradication of selection bias has not been achieved yet. This pilot study aims to not only highlight the importance of accuracy, precision and adherence to treatment protocols and recording data, but also to help form Bangladesh's very own GBM treatment framework based on secondary analysis of existing data. It can serve as the first steps to the publication of realistic, globally accepted, clinical protocols paperwork for other LMICs. This study will focus on the molecular markers IDH1, Ki-67, and MGMT and investigate a variety of marker combinations from each sample to encourage the advancements of neurology and oncology in Bangladesh. IDH1 mutation is found to be inversely associated with tumor progression [4]. Ki-67, a nuclear protein in proliferating cells, serves as a marker for tumor growth rate, with higher levels indicating more aggressive tumors [5]. MGMT promoter methylation predicts response to TMZ and is to be an exploratory biomarker [14]. The aim of this pilot study is to evaluate how these markers, along with clinical factors and treatment adherence, relate to GBM recurrence in Bangladeshi patients, providing data to improve clinical management, increase post surgery overall median survival chances and serve as foundation for more in-depth research on GBM, both domestically and globally.

### **Research Questions:**

1. How do molecular markers affect the likelihood of GBM recurrence in Bangladeshi patients? 25
2. What are the combined effects of IDH1 mutation, MGMT promoter methylation, and Ki-67 proliferation index on GBM prognosis?
3. Are global data consistent with Bangladeshi patient profiles?
4. How can individual data be used to increase median post-operative survival probability?

- Are current treatment protocols appropriate for varying marker combination profiles and patient histories?

#### **Literature Review:**

In high-income countries, adherence and completion of treatment are generally more prevalent, alongside more effective medical care and facilities, compared to LMICs such as Bangladesh. Research combining IDH1, MGMT and Ki-67 with clinical, surgical, and lifestyle data in Bangladesh is limited, despite its importance for effective treatment. Zeng et al. (2015) found that combining IDH1/2 mutation status with Ki-67 improved prognostic stratification of gliomas [7]. This study has stellar findings that draw a conclusion of correlation of molecular markers and GBM recurrence, however, it did not include Bangladeshi patients or local treatment variations, therefore, does not take into account differences in patient profiles due to demographic factors, ethnicity and differences in availability of effective and precise medical facilities and procedures. Armocida et al. (2020) reported that Ki-67 overexpression predicts shorter progression-free survival in IDH-wildtype glioblastomas [8]. On the other hand, without assessing IDH1-mutated tumors, solid conclusions regarding the combination of both variables cannot be made. A study was done to scale and predict post-surgery survival which, while providing imperative information, did not explicitly study molecular markers [6]. Aberrant IDH1 expression, particularly with p53, is associated with distinct survival outcomes as studied by Meet et al. [9]. MGMT methylation globally predicts chemotherapy response and survival [14]. Neither of these has been studied in combination with other markers and clinical characteristics and demographic in Bangladesh. A study by Sarkar et al. (2023) states that 17.14% of glioblastoma cases in Bangladesh showed IDH1 expression, mostly IDH-wild type, consistent with global trends [11]. However, Ki-67 proliferation was not explored. Mondal et al. (2016) found astrocytic tumors are the most common in Bangladesh, with GBM (WHO Grade IV) predominating [12]. Amongst extensive global studies, few have combined molecular, clinical, lifestyle, and treatment history in Bangladeshi GBM patients. Lack of region specific data and over-generalization of medical cases across the globe can lead to poor treatment and QoL. This study aims to identify patterns and correlations to improve prognosis and patient management in Bangladesh and improve overall patient care and contribute towards domestic in-depth research on GBM.

#### **Methodology:**

This study will adopt a retrospective cohort design, conducted as a pilot study to support future, larger scale studies. Patients, including adults (>18 years) diagnosed with primary GBM who underwent surgical resection will be studied from multiple institutions across the country, sample size depending on number of patients who fit the eligibility criteria. Those with metastatic tumors, incomplete records, or death within 30 days post-surgery will be excluded. IHC will be performed on FFPE tumor samples to collect data on molecular markers.

Data Collection: Patient data from early 2018 to late 2024, including demographical (age, sex, marital status, etc) data, clinical and histological characteristics and records, numbers of resections, marker tests (IDH1, Ki-67, MGMT), treatment adherence (Stupp Protocol), recurrence outcomes, follow up plans and schedules in accordance with MRI Scans etc will be collected from multiple hospitals, including BSMMU and NICRH, following IRB and ethical

approval. A REDCap questionnaire will be used to systematically record aforementioned variables to ensure accuracy and proper organisation and comparison of data.

Dependent Variable: Tumor recurrence (binary outcome: yes/no; time to recurrence)

Independent Variable: Age, sex, BMI, molecular markers (IDH1, Ki-67, MGMT), comorbidities, adherence to treatment protocol

Confounding variables: Lifestyle factors, pre-existing medical conditions

Descriptive Statistics (mean, median, standard deviation and percentage) will show distribution and summarize patient demographics, clinical characteristics, and recurrence rates.

Inferential statistics will be used to evaluate distribution based associations between independent variables and recurrence via Chi-square tests for categorical variables and T-tests or Mann-Whitney U tests for continuous variables.

Survival Analysis, i.e., Kaplan-Meier curves for all 3 markers will illustrate time-to-recurrence, and the Log-rank test will compare recurrence between groups. Cox proportional hazards regression will determine the effect of each independent variable on recurrence while controlling for confounders. Visual representation of data can lead to improved understanding of patterns and clinical response will change accordingly.

Analyses will be performed using the softwares: SPSS & R.

Potential limitations include missing data, which will be cross-verified or imputed, small sample sizes addressed by combining datasets from multiple hospitals, and variations in follow-up schedules accounted for via time-to-event analysis. Disruptions caused by the COVID-19 pandemic may have affected patient follow-up and adherence to treatment protocols, potentially influencing recurrence outcomes, so the most accurate, complete data by comparison will be selected. Ethical concerns will be managed by anonymizing and deidentification of patient data and reporting aggregated results.

#### **Expected Outcomes:**

The study will display the rate and timing of GBM recurrence in Bangladeshi post-operative patients via Kaplan-Meier curves for all three markers. High Ki-67 is expected to correlate with faster recurrence, IDH1 mutation with longer progression-free survival, and MGMT methylation with improved treatment response. Combining these markers may improve prognostic stratification and guide personalized monitoring. Possible correlations between clinical and demographic factors, treatment adherence, and recurrence will be shown. The findings will establish a foundational dataset for Bangladesh, supporting genomic analyses, and predictive modeling of GBM outcomes. It will also improve follow-up strategies, early intervention, survival outcomes, prognosis and treatment planning frameworks.

#### **Conclusion:**

This study integrates molecular markers (IDH1, Ki-67, MGMT) with clinical and demographic factors to uncover post-operative GBM recurrence patterns in Bangladesh. Addressing gaps in

region-specific data, will identify high-risk patient profiles, inform follow-up strategies, lay down a framework for treatment and protocol for specific marker combination and provide a foundation for future global and domestic research on molecular mechanisms, treatment adherence, and clinical management. The findings are expected to serve as a foundation for future research in a way not previously studied in Bangladesh, contributing to global knowledge on GBM recurrence, vitality of researching, treatment adherence importance and strategies, limitations and shortcomings to be addressed, etc from an understudied LMIC perspective.

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