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Equity in Focus : Investigating Gender Disparities in Glioblastoma via Propensity Score Matching

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Abstract

Background: Gender disparities in health outcomes have garnered significant attention, prompting investigations into their underlying causes. Glioblastoma (GBM), a devastating and highly aggressive form of brain tumor, serves as a case for such inquiries. Despite the mounting evidence on gender disparities in GBM outcomes, investigations specific at the molecular level remain scarce and often limited by confounding biases in observational studies.

Methods: In this study, I aimed to investigate the gender-related differences in GBM outcomes using propensity score matching (PSM) to control for potential confounding variables. The data used was accessed from the Cancer Genome Atlas (TCGA), encompassing factors such as gender, age, molecular characteristics and different glioma grades. Propensity scores were calculated for each patient using logistic regression, representing the likelihood of being male based on the baseline characteristics. Subsequently, patients were matched using the nearest-neighbor (with a restricted caliper) matching to create a balanced male-female group.

Results: After PSM, 303 male-female pairs were identified, with similar baseline characteristics in terms of age and molecular features. The analysis revealed a higher incidence of GBM in males compared to females, after adjusting for potential confounding factors.

Conclusions: This study contributes to the discourse on gender equity in health, paving the way for targeted interventions and improved outcomes, and may guide efforts to improve gender-specific treatment strategies for GBM patients. However, further investigations and prospective studies are warranted to validate these findings and explore additional factors that might contribute to the observed gender-based differences in GBM outcomes aside from the molecular characteristics.

Keywords: glioblastoma; propensity score matching; brain tumor; gender disparities; molecular characteristics; confounding factors

1 Introduction

Gliomas are highly aggressive primary brain tumors (with a rapid progression rate), originating from glial cells. They are highly heterogeneous in nature, exhibiting diverse molecular characteristics and clinical outcomes [1, 2]. These tumors can cause severe neurological impairments and are the most prevalent type of primary brain tumor [3, 4]. While gliomas occur relatively infrequently with an incidence rate of approximately less than 10 cases per 100,000 population [5, 6, 7], they pose significant challenges

in diagnosis, treatment and prognosis due to their variable aggressiveness and clinical behavior. As a result, accurate classification is of utmost importance for effective treatment planning and personalized patient care.

Traditionally, glioma grading has relied on the World Health Organization (WHO) grading system and histological features [1, 8, 9, 10], such as cellular atypia, mitotic activity and vascular proliferation. However, due to interobserver variability, histopathological assessment alone may not always offer a comprehensive understanding of the underlying molecular alterations that fuel glioma growth and affect patient prognosis [1, 11].

Recent advancements in molecular profiling techniques have provided valuable insights into the underlying biology of glioma, leading to the identification of several molecular markers associated with different glioma grades. Molecular characteristics, including genetic alterations, epigenetic modifications and DNA methylation patterns, have emerged as essential components for understanding the molecular basis of glioma progression and prognosis [12, 13, 14]. Integration of these molecular characteristics with traditional histopathological features has the potential to enhance the accuracy and reliability of glioma grading.

Numerous studies have significantly contributed to the advancement of glioma grading by highlighting the prognostic significance of specific molecular biomarkers. These findings have facilitated a more precise assessment of tumor behavior and improved patient management in both glioma research and clinical practice. One pivotal molecular marker in glioma grading is the isocitrate dehydrogenase (IDH) mutation status. Mutations in the IDH1/2 genes are frequently observed in lower-grade gliomas (grades II and III) and have been associated with better overall survival and a more favorable prognosis [15, 16, 17, 18]. Alongside IDH mutations, other molecular alterations such as 1p/19q codeletion, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, and epidermal growth factor receptor (EGFR) amplification have also emerged as crucial molecular characteristics linked to glioma grading [19, 20, 21, 22]. The identification and understanding of these molecular markers have paved the way for improved diagnostic and prognostic approaches in glioma research.

Despite advances in medical science and treatment modalities, the prognosis for glioblastoma (GBM) remains dismal [23, 24, 25]. Among the various challenges faced in managing this devastating disease, there is growing evidence suggesting that gender-based disparities significantly impact GBM outcomes. These disparities in disease incidence, prognosis and treatment outcomes raise critical concerns about potential underlying factors that may contribute to differential outcomes based on gender.

Gender disparities in cancer have long been a topic of interest in oncology research. Multiple studies have demonstrated differing cancer incidences, prognoses and responses to treatments between males and females [26, 27, 28, 29, 30]. While some of these differences can be attributed to variations in lifestyle factors and hormonal influences, emerging evidence suggests that intrinsic biological and genetic disparities may also play crucial roles. Furthermore, social and cultural factors might influence healthcare-seeking behavior, treatment decisions and adherence, thereby contributing to divergent GBM outcomes between genders.

Despite the mounting evidence on gender disparities in cancer, comprehensive investigations specific to GBM remain scarce and often limited by confounding biases in observational studies. Observational

study is an empirical investigation in which the objective is to elucidate cause-and-effect relationships when it is not possible to impose procedures or treatments whose effects are desired to discover, or assign subjects at random to different procedures [31]. The absence of random treatment assignment often leads to systematic differences between treated and control subjects at the beginning of the study. This confounding factor makes it challenging to directly compare outcomes between the two groups. To address this issue, statistical methods involving the propensity score are becoming more prevalent in observational studies investigating treatment effects. Propensity Score Matching (PSM) offers a robust statistical approach to mitigate such biases, facilitating a more accurate evaluation of gender-based differences in GBM outcomes [32, 33]. It is a non-randomized method that facilitates the creation of balanced groups from observational data by estimating the likelihood of an individual being assigned to a particular condition [34, 35, 36, 37]. By matching patients based on their propensity scores (the likelihood of being assigned to a particular gender, given their baseline characteristics), I seek to minimize the impact of confounders and obtain reliable estimates of gender-specific disparities in GBM outcomes.

As a result, I present an examination of gender-based disparities in GBM by employing PSM on a meticulously characterized patient cohort. The study sought to explore and understand the fundamental variations in baseline demographics and molecular profiles between male and female GBM patients. Furthermore, I aimed to evaluate the influence of gender on GBM incidence rates. Leveraging the power of PSM, I effectively addressed potential confounding factors and selection biases, thereby ensuring the reliability and objectivity of my findings regarding gender-related disparities in GBM. By shedding light on these aspects, this work contributes valuable insights into the complex interplay of gender and GBM, with potential implications for personalized treatment strategies and targeted interventions in the future.

2 Literature Review

GBM poses significant challenges in patient management and treatment due to its heterogeneous nature. Over the years, research efforts have sought to identify potential factors contributing to the variable outcomes observed in GBM patients. One aspect of particular interest is the exploration of gender-based disparities in GBM outcomes. Here, I review some relevant literature to provide an overview of previous studies investigating gender-related differences in GBM.

Diaz et al. [38] conducted a comprehensive analysis of gender disparities in glioma research, focusing on the representation and analysis of women's data. The authors thoroughly examined the origins of data in this area, shedding light on the concerning underrepresentation of women in both study samples and omics analyses. Their investigation extended to the current landscape of GBM clinical trials, where they rigorously explored the presence of sex bias and how study populations were being represented, aligning with the principles of diversity and inclusion. Moreover, the review critically assessed the suitability of existing data sets for meaningful biospecimen and omics analyses aimed at identifying potential sex differences. The outcome of their research revealed that glioma datasets suffer from an uneven distribution of male and female participants, significantly impacting the generation of accurate and comprehensive conclusions. These challenges in data acquisition and analysis were found to be attributed to health disparities and the limited inclusion of women in both established and emerging data sets, leading to difficulties in characterizing genomic and proteomic connections with sufficient statistical power. To address these critical issues, the authors put forward a strategic proposal for study

design and analysis. Their approach emphasized the need for separate omic characterization of male and female subjects, thereby harnessing potentially meaningful sex differences. In their concluding remarks, the authors underscored the significance of rectifying sex bias in clinical trials and retrospective data sets to ensure equitable and effective treatments for all patients, particularly in the underrepresented sex. Their findings serve as a compelling call-to-action, highlighting the necessity of fostering greater inclusivity and diversity in glioma research to achieve improved patient outcomes.

Similarly, Carrano et al. [39] provided critical insights into understanding GBM at both the phenotype and molecular levels. The aims of their comprehensive review were to elucidate the disparities in GBM between men and women and to identify the molecular pathways that may influence differential outcomes in this tumor. Their findings collectively revealed well-established differences in GBM incidence and outcome between male and female patients, with males exhibiting a higher incidence and worse prognosis compared to their female counterparts. Notably, estrogen was recognized for its protective role, while the upregulation of androgen receptors and testosterone appeared to have detrimental effects on GBM progression. The interplay between hormones and the immune system was identified as a crucial factor directly influencing the GBM microenvironment. Additionally, recent discoveries highlighted specific genes and molecular pathways that are differentially regulated depending on the sex of the patient, potentially playing a significant role in determining GBM outcomes. These results underscore the importance of considering sexual dimorphism in GBM and advocate for an individualized approach to patient management, particularly regarding the molecular level differences that impact treatment strategies.

Another notable study by Khan et al. [40] identified gender-specific molecular differences in GBM and LGG using transcriptomic and epigenomic datasets from the Cancer Genome Atlas (TCGA) and Chinese Glioma Genome Atlas (CGGA) databases. They studied the transcriptomic profile in TCGA using DeSeq2 and in CGGA using T-test, after correction based. They also used weighted gene co-expression network analysis (WGCNA) to identify differentially affected signaling pathways and assessed modular differential connectivity. Their analysis revealed gender-based disparities in GBM and LGG, highlighting differentially expressed genes with varying impacts on survival. Additionally, they explored gender-specific epigenetic variations through DNA methylation analysis. They concluded that their study provides an insight into targeting glioma in a gender-specific manner, as both males and females have differential connectivity in various biologically relevant pathways.

Furthermore, Yang et al. [41] investigated sex differences in cancer biology by analyzing patient imaging, transcriptome and survival data of male and female GBM patients. Their objective was to evaluate gene signatures' prognostic value in male and female primary GBM cell lines and explore the correlation between specific gene expression and IC50 values. Additionally, the researchers sought to understand the mechanisms underlying sex-specific survival benefits and compared the survival and transcriptome expression of certain genes between male and female GBM patients. The study's outcomes suggested that sex-specific, cell-intrinsic responses to the loss of p53 function may render male astrocytes more vulnerable to malignant transformation compared to females. These findings shed light on the observed sex differences in glioma incidence and highlight sexual dimorphism in the p53 pathway. The paper emphasized the significance of considering sex differences in cancer biology and clinical response, offering potential avenues for personalized approaches in cancer research and treatment.

These literature demonstrates an emerging interest in investigating gender-based disparities in GBM outcomes. The studies reviewed provide valuable insights into potential factors that might contribute to observed differences in survival rates, treatment responses and tumor biology between male and female patients. However, it is essential to acknowledge the limitations of retrospective studies and potential confounding variables, which warrant further investigation through a well-controlled studies.

As I embark on my own study utilizing propensity score matching to explore gender-related differences in GBM outcomes, it is imperative to build upon the existing literature and contribute to a better understanding of this complex disease. By carefully addressing potential confounding variables and employing robust statistical methods, I hope to provide meaningful insights that can inform the development of gender-specific treatment strategies and improve patient outcomes in the battle against GBM.

3 Materials and Methods

3.1 Data Description

The data used in this investigation is sourced from TCGA [9, 42], a publicly available repository of cancer genomics data. It comprises a rich collection of both clinical and some frequently mutated molecular features, complemented by class labels representing glioma grading (Table 1). These molecular features are represented as binary values, where "not_mutated" (wildtype) is denoted by 0 and "mutated" by 1 based on the TCGA Case_ID, providing valuable insights into the genetic mutations associated with glioma. The class labels in the dataset are assigned to indicate the glioma grading, which can be categorized into two groups: LGG and GBM. These labels serve as the target variable for the analysis, enabling the assessment of the severity and aggressiveness of the brain tumors. In total, the dataset comprises 839 instances, providing a substantial amount of data for the analysis of brain tumor grading. This dataset offers valuable information for understanding the genetic and clinical factors associated with glioma progression and may contribute to the development of improved diagnostic and treatment approaches.

Table 1: Selected subset of the clinical and molecular features used in the analysis.

#	Feature	Type	Domain	#	Feature	Type	Domain
1	Age	Numerical	≥18	8	BCOR	Categorical	0, 1
2	Gender	Categorical	0, 1	9	MUC16	Categorical	0, 1
3	IDH1	Categorical	0, 1	10	PIK3R1	Categorical	0, 1
4	ATRX	Categorical	0, 1	11	PDGFRA	Categorical	0, 1
5	PTEN	Categorical	0, 1	12	CSMD3	Categorical	0, 1
6	EGFR	Categorical	0, 1	13	IDH2	Categorical	0, 1
7	CIC	Categorical	0, 1	14	FAT4	Categorical	0, 1

Class information: Grade (0 : LGG, 1 : GBM)

3.2 Statistical Analysis

Categorical outcomes were expressed as frequency (percentage). Then, PSM was performed on the selected dataset. The propensity score (PS) was estimated using a logistic regression model (defined by Equation 1) with 1:1 nearest neighbour matching. However, there is a potential challenge which arises when the nearest neighbor happens to be significantly distant, leading to less-than-desirable matches. To address this concern, I introduced a caliper constraint set at 0.25 times the standard deviation of the PS. This was done to establish an acceptable limit for the maximum permissible PS distance. As a result, only nearest neighbors that fell within this caliper range were taken into consideration for the matching process. The goal was to create pairs of patients with similar PS, ensuring comparability between male and female groups. Once the matched-pairs were created, it was necessary to access the balance achieved in the covariates between the male and female groups. As a result, the matching ability of the PSM was assessed by the standardized mean difference (SMD) that is not affected by the samples size and represents properties of the sample [43], indicating the balance of covariates between male and female groups before and after PSM. I calculated the SMD for each covariate to quantify the magnitude of gender-related differences. A threshold $|\text{SMD}| \leq 0.1$ was considered insignificant or balanced (a reduced effect size) in the analysis [44, 45].

$$\begin{aligned}\text{logit}\,(p_m) = \; & \alpha + \alpha_1(\text{Age}) + \alpha_2(\text{IDH1}) + \alpha_3(\text{ATRX}) + \alpha_4(\text{PTEN}) + \alpha_5(\text{EGFR}) + \alpha_6(\text{BCOR}) + \alpha_7(\text{PDGFRA}) \\ & + \alpha_8(\text{CIC}) + \alpha_9(\text{PIK3R1}) + \alpha_{10}(\text{CSMD3}) + \alpha_{11}(\text{IDH2}) + \alpha_{12}(\text{FAT4}) + \alpha_{13}(\text{MUC16}) \end{aligned} \tag{1}$$

where, p_m represents the probability of being a male.

With the matched groups, the association between gender and GBM outcomes was examined without the confounding effects of imbalanced covariates. The odds ratio (using a logistic model) and effect estimates were calculated while accounting for confounders. The average treatment effect (ATE) was calculated by finding the difference in the mean outcome of GBM outcomes between the male and female groups. Extending beyond ATE, the reporting of the Average Treatment Effect on the Treated (ATT) and the Average Treatment Effect on the Control (ATC) assumed paramount significance. The ATC estimated the average incidence of GBM within the control group (specifically, females) under the hypothetical scenario of being males. Conversely, the ATT estimated the average GBM incidence within the treated group (specifically, males), attributable to the condition of being male. These estimations helped to gain insights into the gender effects within the subgroups and better understand the differential impact on GBM outcome.

4 Results and Discussions

Table 2 presents the demographic features of patients with different glioma grades, specifically LGG and GBM. The table highlights key variables including gender distribution, mutation of molecular markers (IDH1, ATRX, PTEN, EGFR, BCOR, CIC, MUC16, PIK3R1, CSMD3, IDH2, FAT4, PDGFRA), and the average age with standard deviation for each group.

Among the total cohort of 839 patients, 41.84% were male. Upon examining the distinct glioma grades, it was revealed that 44.35% of patients with LGG and 38.35% of those with GBM were male.

Table 2: Demographic and molecular features of patients categorized according to glioma grades

Variable	**Total (N = 839)**	**LGG (N = 487)**	**GBM (N = 352)**
Gender = Male (%)	351 (41.84)	216 (44.35)	135 (38.35)
IDH1 = 1 (%)	404 (48.15)	381 (78.23)	23 (6.53)
ATRX = 1 (%)	217 (25.86)	183 (37.58)	34 (9.66)
PTEN = 1 (%)	141 (16.81)	25 (5.13)	116 (32.95)
EGFR = 1 (%)	112 (13.35)	31 (6.37)	81 (23.01)
BCOR = 1 (%)	29 (3.46)	17 (3.49)	12 (3.41)
CIC = 1 (%)	111 (13.23)	107 (21.97)	4 (1.14)
MUC16 = 1 (%)	98 (11.68)	41 (8.42)	57 (16.19)
PIK3R1 = 1 (%)	54 (6.44)	21 (4.31)	33 (9.38)
CSMD3 = 1 (%)	27 (3.22)	12 (2.46)	15 (4.26)
PDGFRA = 1 (%)	22 (2.62%)	6 (1.23%)	16 (4.55%)
IDH2 = 1 (%)	23 (2.74)	21 (4.31)	2 (0.57)
FAT4 = 1 (%)	23 (2.74)	11 (2.26)	12 (3.41)
Age, mean (SD)	50.94 (15.70)	43.87 (13.26)	60.70 (13.43)

Figure 1 shows the distribution of propensity scores (for being in the male group) in the two groups before and after PSM. It was observed that before PSM, there was a significant difference between the distribution of propensity scores in the male and female groups. However, the distribution of propensity scores in the two groups appeared to be more similar after PSM, indicating that the matching was effective in reducing imbalance in the distribution of propensity scores between the two groups.

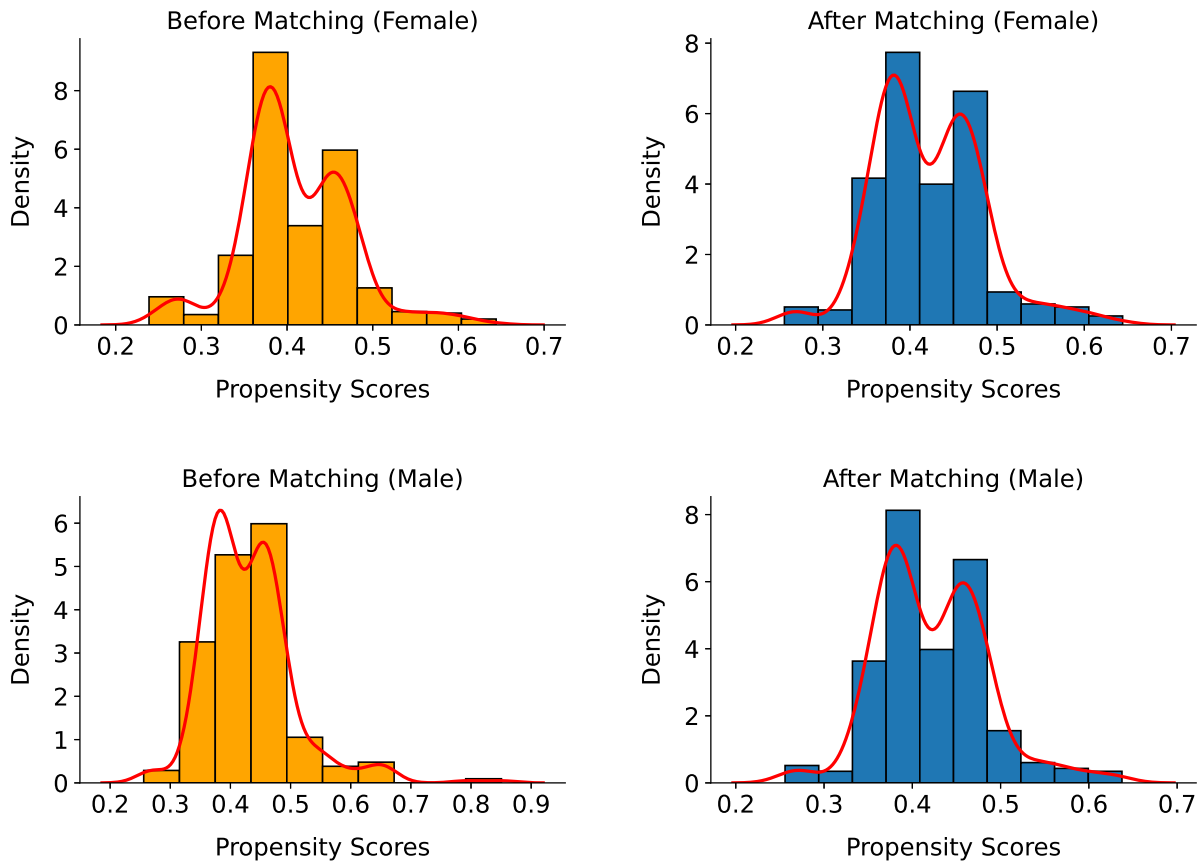

Figure 1: Distribution of the estimated propensity scores for male and female patients before and after matching. The left panel displays the distribution of propensity scores before matching, highlighting potential imbalances between male and female cohorts. The right panel shows the distribution after matching, demonstrating the improved balance achieved between the two groups.

Table 3 provides a detailed overview of the covariates, represented as proportions within both male and female cohorts before and after the matching process. The SMD was computed for each covariate to assess the extent of differences between the male and female cohorts for each covariate.

Prior to matching, it was observed (from Table 3) that a few molecular markers exhibited notable differences between male and female participants. Particularly, ATRX, BCOR, CIC, PIK3R1 and FAT4 demonstrated higher SMD values (greater than 0.1), suggesting substantial gender-related disparities in their mutation. However, after matching, a remarkable reduction in SMD values for these markers was observed, indicating effective mitigation of gender-related confounding effects.

I also analyzed the age distribution in both cases to account for potential age-related effect. Notably, the age difference between male and female participants was found to be relatively small even before matching, indicating a balanced age distribution. Post-matching, the age distribution remained comparably balanced, further corroborating the success of the matching strategy.

The results from the "After Matching" dataset suggest that the molecular features and age for male and female participants are now more comparable, which strengthens the validity of any subsequent

analyses or conclusions drawn from the study. The reduced SMD values after matching indicate that gender differences in molecular markers have been mitigated, potentially improving the accuracy and reliability of the study's findings.

Table 3: Comparison of clinical and molecular features before and after matching by gender

	Before Matching			**After Matching**		
Feature	**Male (n=351)**	**Female (n=488)**	**|SMD|**	**Male (n=303)**	**Female (n=303)**	**|SMD|**
IDH1 (%)	50.997	46.107	0.098	53.465	51.485	0.040
ATRX (%)	28.775	23.770	0.114	27.723	28.713	0.022
PTEN (%)	15.385	17.828	0.065	14.191	16.832	0.073
EGFR (%)	11.966	14.344	0.070	11.221	12.211	0.031
BCOR (%)	5.128	2.254	0.158	2.970	2.640	0.020
CIC (%)	15.670	11.475	0.124	14.521	13.861	0.019
MUC16 (%)	12.251	11.270	0.030	11.881	10.891	0.031
PIK3R1 (%)	4.843	7.582	0.112	4.620	4.290	0.016
PDGFRA (%)	3.134	2.254	0.055	2.310	2.640	0.021
CSMD3 (%)	3.989	2.664	0.075	2.970	3.300	0.019
IDH2 (%)	3.134	2.459	0.041	2.640	2.970	0.020
FAT4 (%)	3.989	1.844	0.131	2.310	2.640	0.021
Age, mean (SD)	50.63 (15.57)	51.15 (15.81)	0.033	49.92 (15.47)	50.13 (15.57)	0.014

Figure 2 also illustrates the achieved balance in the matched dataset, as gauged by the SMD metric for each covariate. Evidently, the matching process resulted in substantial balance across all covariates, with the largest absolute standardized difference approaching 0.08. As a result, any gender-related disparities within the overlapping population, which could impact GBM outcomes, have effectively been mitigated.

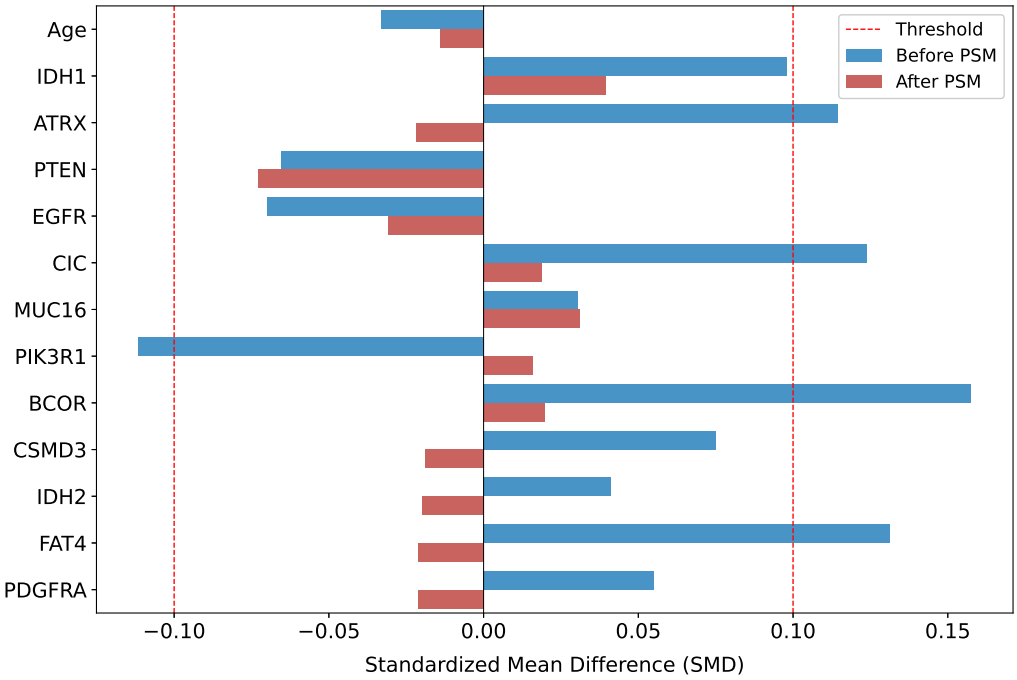

Figure 2: Comparison of standardized mean difference for each covariate in both the original and matched datasets. The vertical dotted red lines represent the balance threshold at −0.1 and 0.1, indicating the target range for covariate balance achieved through the matching process.

Subsequent to confirming the balanced distribution of covariates between the male and female cohorts via the PSM procedure, I conducted an outcome analyses to delve into the influence of male gender on the incidence of GBM.

It was observed that patients identifying as male exhibited higher odds of being diagnosed with GBM when compared to their female counterparts. The calculated odds ratio (OR) of 2.069 illuminated this association, indicating that males were approximately 2.069 times more likely to have GBM than females. This was further supported by the 95% confidence interval spanning from 1.039 to 4.118, which not only excluded the null value of 1 but also attested to the statistical significance of the observed association. This significance was further supported by a p-value less than 0.05, signifying a less than 5% likelihood of this association arising due to random chance.

Additionally, Table 4 presents the effect estimates on GBM outcome after PSM. ATE, ATT and ATC were reported along with their corresponding standard errors, p-values, and 95% confidence intervals. The estimated ATE of 0.497 ± 0.085 (95% CI: 0.330, 0.664; p-value < 0.05) obtained from logistic regression analysis indicates a statistically significant effect of being a male on GBM outcome. The positive ATE value signifies that, on average, patients who were identified as males had higher chances of developing GBM compared to those who were females. The 95% confidence interval provided a range within which the true treatment (being a male) effect is likely to lie, with values consistently above zero, indicating a consistent increase in GBM incidence. The small standard error indicated less variability and provided greater precision in estimating the ATE value.

Similarly, both the ATT and ATC estimates also demonstrated statistically significant positive effects of

being a male on GBM incidence. This implies that between the two groups, being a male was associated with a high risk of developing GBM. The 95% confidence intervals indicated a high level of confidence in the precision of the effect estimates. The p values being less than 0.05 further supported the statistical significance of the observed effects. Taken together, these results indicated that males exhibit a notably higher incidence of GBM compared to their female counterparts.

Table 4: Effect estimates and statistical significance obtained after matching

	Estimate	**Standard Error**	**95% Confidence Interval**		**p-value**
ATE	0.497	0.085	0.330	0.664	< 0.05
ATC	0.611	0.096	0.422	0.800	< 0.05
ATT	0.411	0.117	0.190	0.647	< 0.05

5 Conclusion

This study investigated how gender disparities impact the outcome of GBM, taking into account various influential factors such as age and molecular characteristics through PSM analysis. It was revealed that male patients faced a greater susceptibility to GBM development compared to females, after accounting for potential confounding factors. The findings of this study could provide clinicians with informative cues to develop gender-specific approaches for GBM management and treatment, aiming to enhance patient outcomes based on divergent prognostic factors.

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