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Risk prediction and treatment assessment in glioma patients using SEER database: a prospective observational study

XinRong Li ,[1] Yan Shao,[2] ZeMing Wang,[1] JunQuan Zhu[1]

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[1]Department of Integrative Medicine and Medical Oncology, Shengzhou People's Hospital (the First Affiliated Hospital of Zhejiang University Shengzhou Branch), Shengzhou, Zhejiang, People's Republic of China
[2]Department of Pharmacy, Shengzhou People's Hospital (the First Affiliated Hospital of Zhejiang University Shengzhou Branch), Shengzhou, Zhejiang, People's Republic of China

Correspondence to
Dr XinRong Li;
57258782@qq.com

ABSTRACT

Objectives To use a nomogram to predict the risk of mortality and estimate the impact of current treatment on the prognosis of glioma patients.

Methods A total of 3798 cases were obtained from the Surveillance Epidemiology and End Results database according to the selection criteria. A nomogram was built on the independent clinical factors screened by the variance inflation factor, univariate analyses and a multivariate Cox regression model. Then, categorising the overall population into high-risk, medium-risk and low-risk groups using nomogram-derived risk scores, to study the impact of treatment on different subgroups' survival outcomes. Furthermore, based on the postmatch cohorts, the influences of treatment on survival outcomes were assessed by the log-rank test.

Result Age, race, stage of disease, histological type, histological grade, surgery, radiotherapy and chemotherapy were identified as the independent prognostic factors. A nomogram with good discrimination and consistency was built. Generally, the patients who underwent surgery, radiotherapy and chemotherapy were more likely to achieve better prognosis than those who did not, except for those who received radiotherapy in the low-risk cohort and those who underwent surgery in the high-risk cohort. Furthermore, the isocitrate dehydrogenase 1/2 (IDH1/2) wild-type patients with surgery, radiotherapy or chemotherapy tended to have higher survival probabilities, while some inconsistent results were observed in the IDH mutant-type cohort.

Conclusion Surgery, radiotherapy and chemotherapy improved the prognosis, while appropriate selection of topical treatment for the low-risk or high-risk patients deserves further consideration. IDH status gene might be a reliable indicator of therapeutic effectiveness.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Using the Surveillance Epidemiology and End Results database, this study involved multiple centres and a substantial cohort of glioma patients followed over an extended period.
⇒ The concurrent utilisation of inverse probability of treatment weighting and propensity score matching enhances the credibility of analyses conducted on postmatched datasets.
⇒ One limitation is that external validation and an evaluation of clinical utility are necessary before incorporating the nomogram into regular clinical practice.
⇒ Another drawback is the adverse impact of missing information such as tumour size, disease complications and neurological function on result interpretation.

INTRODUCTION

The average annual age-adjusted incidence rate for primary central nervous system (CNS) malignancies in adults (≥20 years old) is estimated to be 8.57 per 100 000 persons. The average annual age-adjusted mortality rates in the USA was 4.37 per 100 000 persons from 2011 to 2015.[1] As the most common intracranial tumour, glioma, could be classified into several heterogeneous tumours with distinct biological and clinical properties, the WHO proposed that the categories should be divided based on the genetic features, rather than only on the histopathological appearance. For example, mutation of isocitrate dehydrogenase 1/2 (IDH1/2) is a defining feature for most low-grade gliomas (LGGs), such as oligodendroglioma and astrocytoma, while the IDH1/2 wild-type is more common in the glioblastoma. In addition to the conventional treatment such as surgery, radiation and temozolomide chemotherapy, the interest in premise strategies based on molecular signatures of the tumour, such as the use of antivascular endothelial growth factor,[2] immune checkpoint inhibitors,[3] integrin inhibitors,[4] dendritic cell vaccines[5] is increasing. Since most of the above approaches are still in the early phase clinical trials and some of preliminary findings are even controversial, the spectrum of options remains narrow. The prognosis could vary significantly based on the different subtypes of gliomas: the 5-year survival rate of glioblastoma is only 6.8%, which is significantly lower than that of the LGGs (eg, 94.4% for pilocytic

astrocytoma[6]). Thus, it is worth establishing a mathematical model containing the molecular signature as well as other cancer-specific factors, including age, race and treatment modalities, etc to predict the prognosis and evaluate the response to the current treatment.

In this study, eligible patients were collected from the Surveillance Epidemiology and End Results (SEER) database (https://seer.cancer.gov/). A nomogram model for estimating survival probabilities was constructed based on the independent risk factors identified by using different statistical approaches. We also evaluated the clinical utility of the model. Furthermore, we used propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) to minimise the distribution bias of the variables, in the postmatch cohorts, we evaluate the impact of surgery, chemotherapy and radiotherapy on the outcomes of glioma patients with and without IDH mutation.

MATERIALS AND METHOD

Patients selection

By using the SEER*Stat software (www.seer.cancer.gov/seerstat, V.8.4.0), patients were obtained from the SEER database (Incidence—SEER Research Plus Data, 17 Registries, Nov 2021 Sub (2000–2019)—Linked To County Attributes—Time Dependent (1990–2019) Income/Rurality, 1969–2020 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2022, based on the November 2021 submission). The selection criteria were as follows: the patients aged ≥18 years, histologically diagnosed as primary brain glioma (one-tumour only) with definitive IDH status. WHO pathological grade records were included. Patients with missing data on race, marital status, disease stage (including 'In Situ'), extent of surgery, survival time, survival status and etc, were excluded. The above operations were done online through the software.

Variable definition

The study collected patients from 2000 to 2019. The survival time was defined as the time from each case's diagnosis to death, lost to follow-up or the December 2019. The variables were categorised into appropriate subgroups. For example, age at diagnosis was divided into four age groups, including 18–49 years, 50–64 years, 65–79 years and ≥80 years. Sex was divided into two levels including male and female. Race was divided into white, black and other races (American Indian/AK Native, Asian/Pacific Islander). Marital status was divided into married or unmarried. Disease stage was divided into localised, regional and distant to exemplify how far a cancer had spread from its point of origin. Histological type was divided into four levels: astrocytoma (IDH wild-type without 1p/19q co-deletion), astrocytoma (IDH mutant-type without 1p/19q co-deletion), oligodendroglioma (IDH mutant-type with 1p/19q co-deletion) and glioblastoma (IDH wild-type without 1p/19q co-deletion). Histological grade was divided into two levels: grades I/II and III/IV. Chemotherapy and radiotherapy were separately divided into 'performed' or 'not performed'. Surgery was divided into three levels including 'surgery not performed', 'subtotal resection' (STR) and 'gross total resection' (GTR).[7] Vital status was divided into 'dead' and 'alive'. If a patient's follow-up time was less than 1 month, the SEER database would set its survival time to 0 months, according to conventional practice.[8 9] This study defined the survival time of these patients as 0.5 months.

Statistical analysis

The patients were randomly divided into training and validation cohorts at a ratio of 7:3. Based on the training set, univariate Cox regression analysis was performed as a preliminarily screen for factors associated with prognosis. Since collinearity might be existed between the variants screened from the univariate Cox regression analysis ($p<0.05$), the variance inflation factor (VIF) values were calculated to measure the degree, and variables with VIF values exceeding 10 were excluded from the next multivariate analysis. Then, a nomogram was constructed based on the pretreatment factors selected from the multivariate Cox regression analysis, excluding treatment information, with a significance level of $p<0.05$. Calibration (with 200 resamples), receiver operating characteristic (ROC) and decision curve analysis (DCA) curves were drawn to estimate the consistency, discrimination and practicability of the nomogram. Subsequently, the whole cohort was divided into high-risk, medium-risk and low-risk sets according to the tertiles of all cases' risk scores estimated by the nomogram, and the influences of the treatment on the survival outcomes were measured by the log-rank test.

Additionally, the population was divided into IDH wild-type and IDH mutant-type cohorts. In order to minimise the distributional bias of variables in the two comparative cohorts, PSM was carried out using an appropriate calliper value (0.05–0.1) and nearest neighbour matching at a 1:1 ratio. This process aimed to estimate the probability, commonly referred to as the propensity score, of an individual receiving a specific treatment of interest, such as surgery, radiotherapy or chemotherapy. This estimation was based on several characteristics, including age, sex, race, marital status, disease stage, histological type, histological grade and two additional treatment options beyond the treatment of interest, such as 'radiotherapy and chemotherapy,' 'surgery and chemotherapy,' or 'surgery and radiotherapy'. These options helped in matching individuals who received treatment of interest to those who did not by discarding certain cases during the process. Given the potential for selective bias, the IPTW was additionally conducted to calculate the weights as inverse of the propensity score based on the factors mentioned above without case censoring, then a pseudo-cohorts with a balanced distribution was created.[10] The frequency of clinical characteristics and the standardised

mean difference of the variables were estimated subsequently. Statistical analyses and graphics representation were conducted using the R software environment (https://www.r-project.org/, V.4.1.3). All statistical tests were two sided and a p<0.05 was considered as significant.

Patient and public involvement

This being a prospective cohort study using SEER data, the glioma patients incorporated into this research were neither actively engaged in the study's design nor subject to recruitment. Furthermore, due to the absence of individually identifiable information, participants will not receive notifications regarding the study's outcomes.

RESULTS

Overall, 3798 patients were obtained from the SEER database. These patients were randomly divided into training cohort (n=2660) and a validation cohort (n=1138) (online supplemental table 1). Based on the training cohort, univariate analyses were performed to identify the prognostic factors among age, race, histological type, histological grade, stage of disease, surgery, radiotherapy and chemotherapy variables. No variable was excluded from the further multivariate analysis since no considerable VIF value was observed (online supplemental figure 1). Multivariate Cox regression analysis identified age, race, histological type, histological grade, stage of disease, surgery, chemotherapy and radiotherapy as independent predictive factors for survival prognosis (table 1).

The nomogram that was developed showed that pretreatment factors, such as increasing age, white race, tumours with IDH wild-type, poor tumour differentiation and advanced disease stage corresponded with an increased probability of all-cause of death (figure 1). Furthermore, the area under the ROC curve estimated on the basis of the nomogram were 0.753, 0.771 and 0.823 for 5-month, 10-month and 20-month survival, respectively, in the training set, and the corresponding values in the validation set were 0.767, 0.78 and 0.814, which indicated good discrimination ability of the model (online supplemental figure 2). The calibration curves for the 5-month, 10-month and 20-month in the training and validation cohorts were all near the diagonal lines which suggested an ideal consistency of the model (online supplemental figure 3). The DCA curves for the 5-month, 10-month and 20-month were all far away from the 'treat-none scheme line', the 'treat-all scheme line' and the 'Summary stage line', which showed that significantly more net benefit was added by using the nomogram to predict the survival probability within the wide threshold intervals (online supplemental figure 4). As indicated by figure 2, in the low-risk category, surgery (figure 2A, p<0.001) and chemotherapy (figure 2B, p<0.001) were found to be associated with improved survival outcomes, while radiotherapy (figure 2C, p=0.16) was not. In the moderate-risk group, all three treatments (figure 2D–F, p<0.001) demonstrated a positive effect on survival. In the high-risk cohort, the relationship between surgery (figure 2G, p=0.056) and prognosis remained unclear, while chemotherapy (figure 2H, p<0.001) and radiotherapy (figure 2I, p<0.001) were linked to enhanced survival.

According to the IDH status, patients were divided into IDH mutant-type (n=754) and IDH wild-type (n=3044) cohorts. After using the PSM and IPTW, the distribution of the most variables were balanced between the groups with and without treatment (online supplemental figures 5 and 6), (online supplemental tables 2–7). For IDH-mutated patients in the prematch cohort, surgery (figure 3A, p<0.001) and chemotherapy (figure 3B, p=0.004) were linked to improved survival outcomes, whereas radiotherapy (figure 3C, p=0.059) was not. In the PSM cohort, there was a tendency for surgery (figure 3D), chemotherapy (figure 3E) and radiotherapy (figure 3F) to be associated with better survival, although these associations did not reach statistical significance. Within the IPTW cohort, surgery (figure 3G, p<0.001) and chemotherapy (figure 3H, p=0.004) were correlated with enhanced survival prospects, while radiotherapy (figure 3I, p=0.057) was not statistically significant. These results indicated that standard treatment might be controversial for the IDH mutant-type patients. Whereas, in the IDH wild-type cohort, the relatively consistent results were observed in the prematch cohort (figure 4A, surgery, p<0.001; figure 4B, chemotherapy, p<0.001; figure 4C, radiotherapy, p<0.001, respectively), PSM cohort (figure 4D, surgery, p=0.018; figure 4E, chemotherapy, p<0.001; figure 4F, radiotherapy, p<0.001, respectively) and IPTW cohort (figure 4G, surgery, p<0.001; figure 4H, chemotherapy, p<0.001; figure 4I, radiotherapy, p<0.001, respectively), which showed that these positive medical interventions were beneficial for IDH wild-type patients. The above results suggested that the IDH status might be a predictor of the therapeutic response and prognostic outcome.

DISCUSSION

Arising from the glial cells of the CNS, gliomas account for 24% of all primary intracranial neoplasms.[11] They are recognised as a heterogeneous set of neoplasms and differ greatly in clinical manifestations, biological characteristics, therapeutic strategies and survival prognosis. With the advent of genetic diagnostic techniques, gliomas could be divided into several distinct categories according to individual histological features and molecular phenotypes. Given this evident tumour heterogeneity, integration of the molecular typing and the conventional clinical characteristics is an essential part of the modern management of the disease, and might facilitate the prognosis prediction, optimise the therapeutic strategies, and offer the potential for improving prognosis. The nomogram we developed here, using demographic and pretreatment factors, initially demonstrates that increasing age, higher historical grade, poorer histological type, and

Table 1 Univariate and multivariate Cox regression analyses on overall survival in the train cohort

	Univariate analysis		P value	Multivariate analysis		P value
Characteristics	HR	95%CI		HR	95% CI	
Age						
18–49 years	1 (Ref)					
50–64 years	3.69	(2.85 to 4.78)	<0.001	1.91	(1.46 to 2.51)	<0.001
65–79 years	7.2	(5.59 to 9.28)	<0.001	3.27	(2.5 to 4.28)	<0.001
≥80 years	16.97	(12.23 to 23.55)	<0.001	5.66	(4.02 to 7.96)	<0.001
Sex						
Female	1 (Ref)					
Male	1.08	(0.94 to 1.24)	0.257			
Race						
White	1 (Ref)					
Black	0.86	(0.65 to 1.15)	0.311	0.81	(0.61 to 1.08)	0.158
Other races	0.66	(0.48 to 0.91)	0.011	0.69	(0.5 to 0.95)	0.023
Marriage						
Unmarried	1 (Ref)					
Married	0.97	(0.84 to 1.11)	0.648			
Histological type						
AST (IDH-wild)	1 (Ref)					
AST (IDH-mutant)	0.15	(0.08 to 0.29)	<0.001	0.35	(0.18 to 0.68)	0.002
OLI (IDH-mutant)	0.12	(0.06 to 0.25)	<0.001	0.26	(0.12 to 0.56)	<0.001
GBM (IDH-mutant)	1.94	(1.39 to 2.7)	<0.001	1.68	(1.19 to 2.37)	0.003
Histological grade†						
I/II	1 (Ref)					
III/IV	16.81	(9.01 to 31.36)	<0.001	6.45	(3.12 to 13.35)	<0.001
Stage						
Localised	1 (Ref)					
Regional	1.62	(1.36 to 1.94)	<0.001	1.82	(1.52 to 2.18)	<0.001
Distant	4.99	(3.08 to 8.09)	<0.001	5.47	(3.35 to 8.91)	<0.001
Surgery						
No	1 (Ref)					
STR	0.47	(0.36 to 0.62)	<0.001	0.74	(0.56 to 0.99)	0.039
GTR	0.31	(0.17 to 0.57)	<0.001	0.58	(0.31 to 1.07)	0.084
Radiotherapy						
No	1 (Ref)					
Yes	0.34	(0.29 to 0.39)	<0.001	0.34	(0.27 to 0.43)	<0.001
Chemotherapy						
No	1 (Ref)					
Yes	0.33	(0.29 to 0.38)	<0.001	0.4	(0.32 to 0.5)	<0.001

*Other races (American Indian/AK Native, Asian/Pacific Islander).
†WHO Grade I; II, WHO Grade II; III, WHO Grade III; IV, WHO Grade IV.
AST, astrocytoma; GBM, glioblastoma; GTR, gross total resection; IDH, isocitrate dehydrogenase; OLI, oligodendroglioma; STR, subtotal resection.

advanced summary stage correspond to higher risk scores and lower survival probabilities. Additionally, by estimating the risk scores for each individual based on the nomogram and stratifying them, the relationship between treatment modalities (surgery, chemotherapy, radiotherapy) and survival outcomes in different risk groups can be investigated, assisting in the determination of treatment indications for glioma. Based on the results,

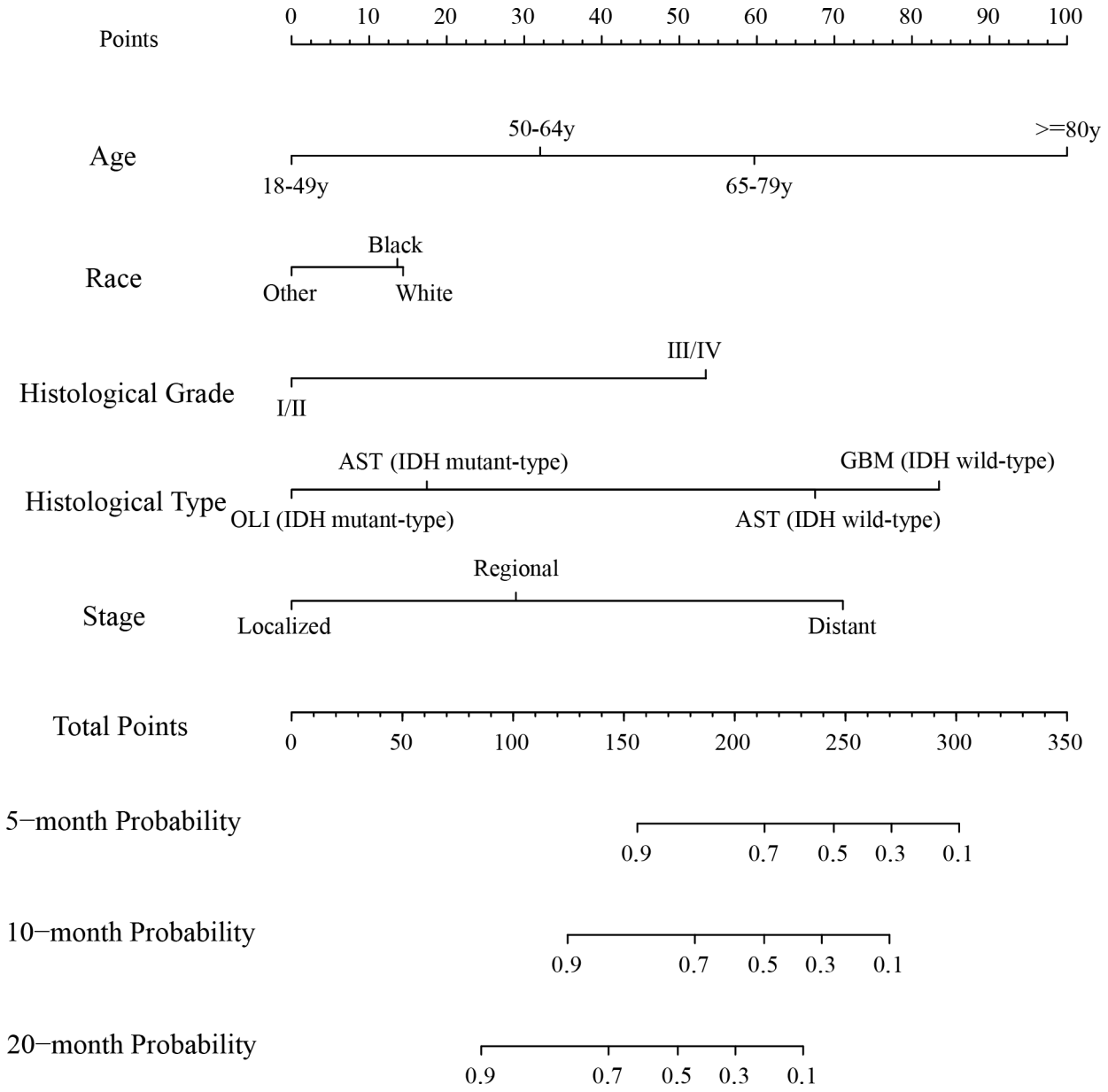

Figure 1 Nomogram to predict 5-month,10-month and 20-month survival probabilities based on the train cohort oligodendroglioma (OLI) (IDH mutant-type): OLI (IDH mutant-type with 1p/19q co-deleted); AST (IDH mutant-type): astrocytoma (IDH mutant-type without 1p/19q co-deleted); AST (IDH wild-type): astrocytoma (IDH wild-type without 1p/19q co-deleted); GBM (IDH wild-type): glioblastoma (IDH wild-type without 1p/19q co-deleted). AST, astrocytoma; IDH, isocitrate dehydrogenase.

in general, surgery, radiotherapy and chemotherapy improved prognosis in glioma patients, but radiotherapy in the low-risk cohort and surgery in the high-risk cohort were not significantly correlated with a good prognosis. Furthermore, it should be noted that although our nomogram exhibited good discrimination, satisfactory consistency and promising decision analysis, external validation and clinical utility assessment are still required before its routine clinical application. To explore the relationship between treatment measures such as surgery, radiotherapy and chemotherapy with regard to the IDH gene's wild-type or mutant status, two methods, PSM and IPTW, were employed to establish comparable population cohorts. As is well known, PSM and IPTW are increasingly used in comparative effectiveness research to address confounding when random treatment assignment is not possible. PSM has limitations like sample loss and subjective matching criteria.[12] Although IPTW overcomes some of these, it is prone to extreme weights. A common approach is to combine these methods for more robust analysis.[13] Based on the matched dataset, it was determined through survival analysis that in the population with non-mutant IDH genes, surgery, chemotherapy or radiotherapy exhibited a significant correlation with improved survival outcomes. Similarly, in the mutant IDH gene population, surgery or chemotherapy was associated with better survival outcomes, although these associations were not corroborated in the PSM dataset, possibly due to

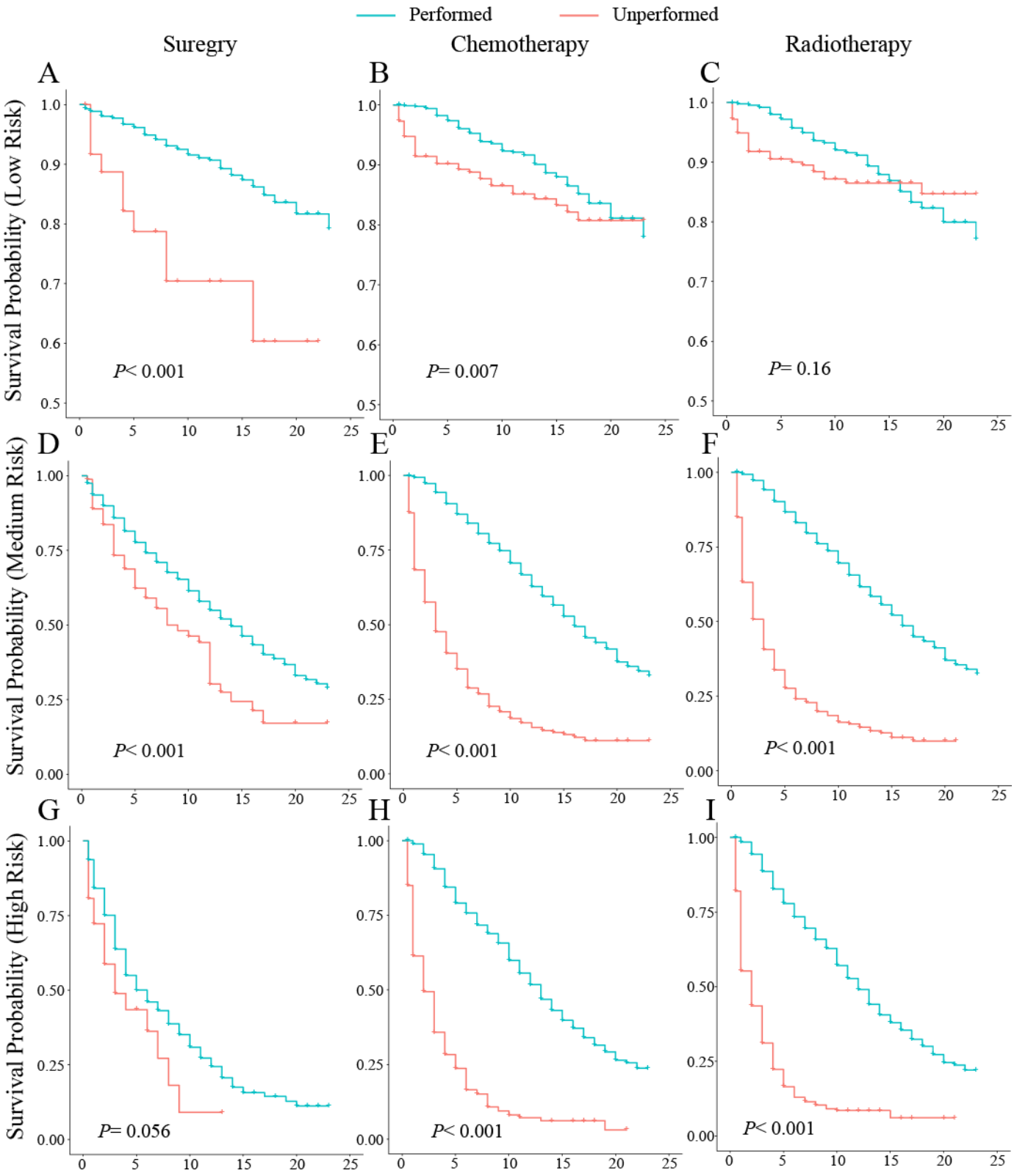

Figure 2 The Kaplan-Meier survival curves of evaluating the influence of treatment on survival probability based on the low-risk cohorts (A, surgery; B, chemotherapy; C, radiotherapy), medium-risk cohorts (D, surgery; E, chemotherapy; F, radiotherapy) and high-risk cohorts (G, surgery; H, chemotherapy; I, radiotherapy).

a substantial loss of sample size during the PSM process. In summary, surgery, radiotherapy or chemotherapy were treatment options for IDH wild-type glioma patients, but no clear conclusions could be drawn about appropriate treatment for IDH mutant-type glioma patients. Through further analysis of the CGGA database (http://www.cgga.org.cn) and using data from two RNA transcriptome sequencing datasets (Dataset ID: mRNAseq_693

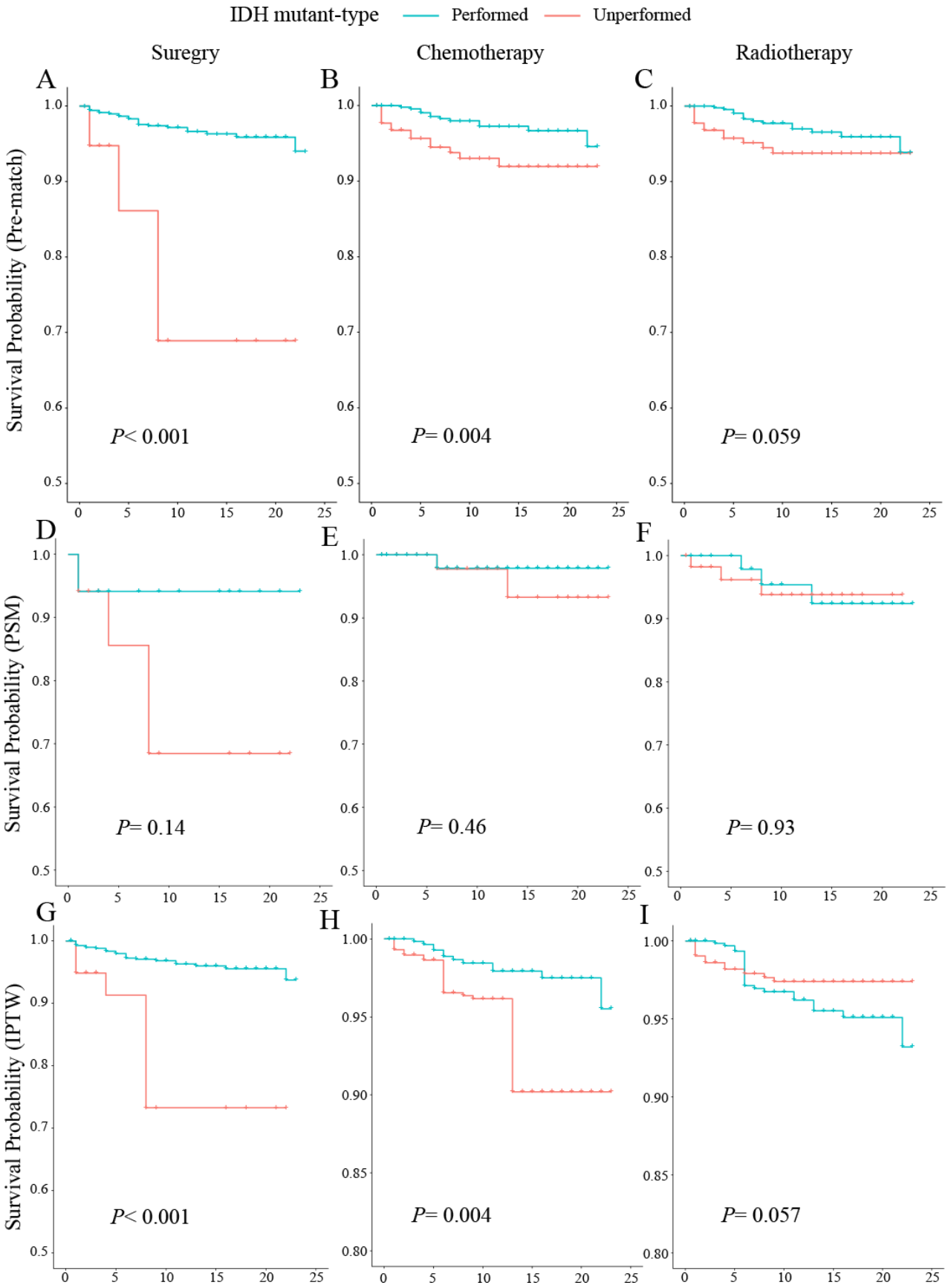

Figure 3 The Kaplan-Meier survival curves of evaluating the influence of treatment on survival probability based on the prematch (A, surgery; B, chemotherapy; C, radiotherapy), PSM (D, surgery; E, chemotherapy; F, radiotherapy) and IPTW (G, surgery; H, chemotherapy; I, radiotherapy) cohorts involving IDH-mutant individuals. IPTW, inverse probability of treatment weighting; PSM, propensity score matching

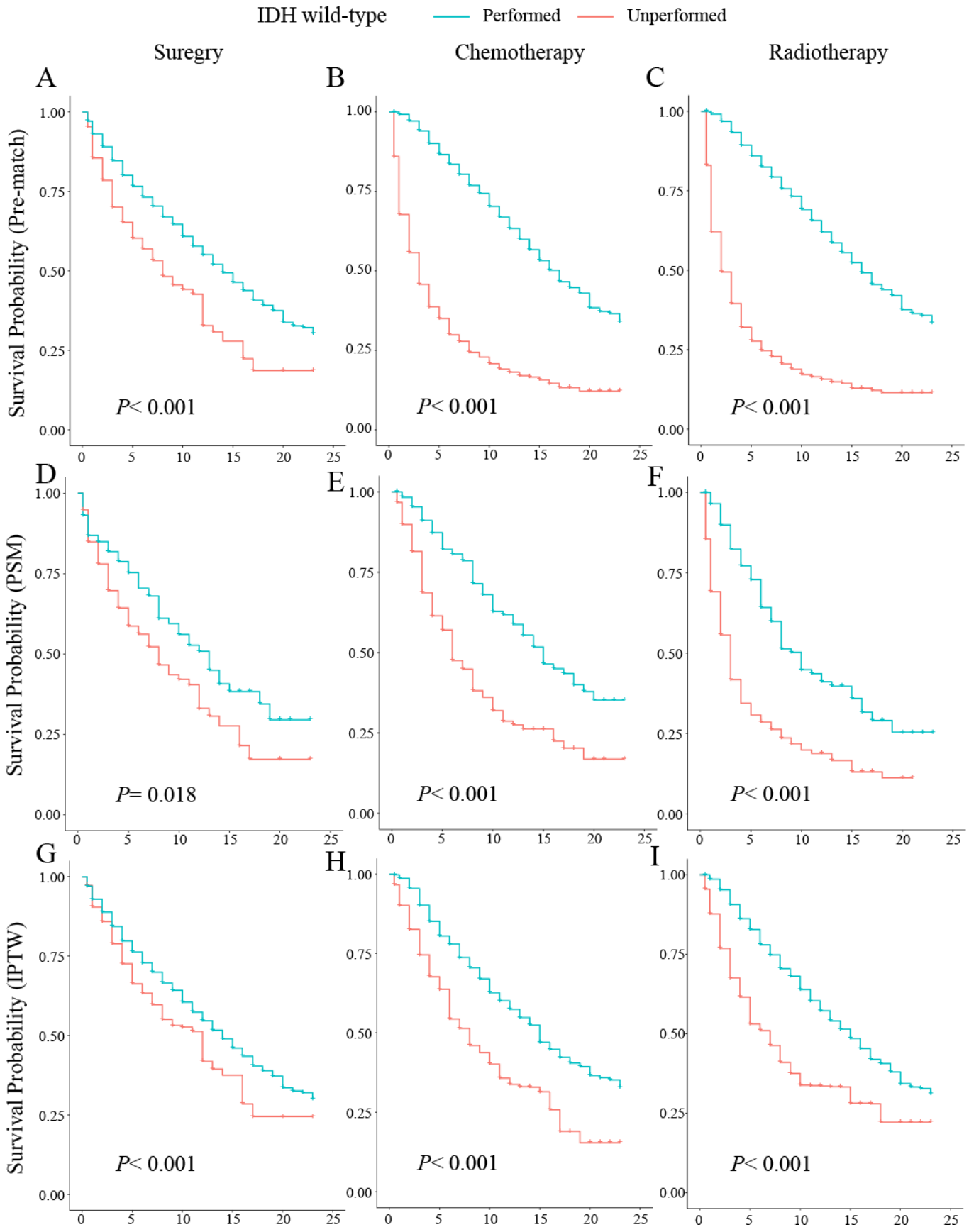

Figure 4 The Kaplan-Meier survival curves of evaluating the influence of treatment on survival probability based on the prematch (A, surgery; B, chemotherapy; C, radiotherapy), PSM (D, surgery; E, chemotherapy; F, radiotherapy) and IPTW (G, surgery; H, chemotherapy; I, radiotherapy) cohorts involving IDH-wild individuals. IPTW: inverse probability of treatment weighting; PSM, propensity score matching.

and Dataset ID: mRNAseq_325), similar conclusions were arrived. According to online supplemental table 8, advanced age, male gender, certain pathological types (such as glioblastoma), more advanced pathological staging, wild-type IDH status and the absence of radiotherapy or chemotherapy administration were associated with a heightened risk of mortality. The results in online supplemental figures 7 and 8 indicated that chemotherapy or radiotherapy tend to have a positive impact on survival outcomes, regardless of the presence of an IDH gene mutation.

Many studies have pointed out that increasing age was an unfavourable prognostic predictor in gliomas. A retrospective study including 548 LGGs patients showed that poor functional status and neurological deficits were more common in older patients with shorter overall survival.[14] Another study also revealed that age at diagnosis was the most important predictor of outcomes of the LGGs patients.[15] In recent years, growing evidence indicated that the relatively aggressive treatment measures might be more beneficial than palliative care.[16] Provided that some essential factors involving physical condition, accompanying symptoms and the adverse effects of treatment are comprehensively considered, radiotherapy associated with concurrent chemotherapy or even the chemotherapy alone was considered to be beneficial for older patients.[17] Therefore, the risks of the disease should be weighed against those of active treatment. In fact, a real-world retrospective study spanning five decades pointed out that older patients did not benefit more from the aggressive strategies, such as GTR and radical STR.[18] Consistently, our study also showed that age was an independent predictive factor for the prognosis in glioma patients, and that the mortality risk gradually increased with age. After adjusting for confounding factors, such as sex and race, the risk of death in glioma patients aged ≥80 years was estimated to be approximately five times greater than that of patients aged 18–49 years. Race was recognised as another key predictor of the survival outcomes in this study. A higher mortality risk was observed in the whites than in blacks and in other racial groups, such as Asian Americans and Pacific islanders. In the USA, the primary CNS malignancies are more common among whites, whose age-adjusted incidence rate was reported as 7.62 per 100 000 population, and is 1.93-fold higher than that of the blacks.[1] Consistently, the mortality risk associated with gliomas among whites was significantly higher than that among other races.[19]

IDH1-R132 mutation is the most common genetic aberrations in glioma. This was first discovered in glioblastoma human samples by next-generation sequencing technologies in 2008.[20] Further research identified IDH2-R172 gene mutation in 2015, which is another relatively rarer mutational subtype of IDH.[21] Studies have indicated that the mutant IDH could promote synthesis of 2-hydroxyglutaric acid, which initiates glioma development by promoting CpG island methylation, impairing T-cell immunity, and inducing HIF-1α.[7 22 23] In addition to the IDH mutation, missense mutation of *ATRX* gene and *TP53* gene are also common in the astrocytomas.[21] Since chromosome 1p/19q co-deletion and the *ATRX* missense mutations are mutually exclusive,[24] the 1p/19q co-deletion is recognised as a molecular feature of the oligodendrogliomas. Generally, according to the status of IDH status and chromosome 1p/19q co-deletion status, gliomas could be divided into different subtypes: IDH mutant-type and 1p/19q co-deleted oligodendroglioma, IDH mutant-type and 1p/19q intact astrocytoma and IDH wild-type glioblastoma. Furthermore, LGGs with IDH mutant-type and IDH wild-type glioblastomas also exist, but are rare.[25] IDH mutant-type glioma is considered to be associated with a better clinical prognosis than IDH wild-type glioma.[21] A similar conclusion could be drawn from our study: patients with mutant IDH tended to have a significantly lower risk of death than did those with wild-type IDH.

Surgical excision is the preferred treatment for the most of gliomas. It has been reported that, even for LGGs, prompt surgical resection was better than regular monitoring.[26] Moreover, a secondary analysis of two large randomised clinical trials indicated that wilder reaction of the lesion might be associated with the better survival outcomes in LGGs patients.[27 28] A similar result was observed in this study, where we found that surgery was beneficial for a good prognosis in low-risk and medium-risk patients. Given the slow growth and low invasiveness of certain LGGs, conservative treatment approaches, like 'watchful waiting,' are occasionally employed.[29] However, a large randomised clinical trial, RTOG 9402 has dispelled the hesitancy of using additional chemotherapy and radiotherapy after surgery for LGGs.[28] Hence, it should be acknowledged that providing chemotherapy and radiotherapy at the opportune time is essential for the management of the glioma.[30] In the study, we found that chemotherapy and radiotherapy were associated with improved survival in medium-risk and high-risk patients. Notably, it was intriguing to observe that surgery alone could be adequate for low-risk patients, and additional local treatments like radiotherapy might not provide additional benefits. Conversely, for high-risk patients, surgery might not be the optimal solution, as even with seemingly complete tumour removal, local recurrence remains common in high-grade glioma patients.

Recent research has delved into the potential connections between gene status and treatment response. The expression of O(6)-methylguanine-DNA-methyltransferase, a DNA repair enzyme that plays a role in resistance to alkylating chemotherapy, can be suppressed by promoter methylation induced by mutant IDH.[31] Therefore, IDH mutant-type gliomas, which are often LGGs, might be more sensitive to temozolomide. Nevertheless, the inconsistency between the actual clinical practice and the guiding principles, and the concerns about long-term adverse effects caused by the treatment, cause standard management of the LGGs to

remain a matter of debate.[29 32] As presented in this study, no significant survival differences between IDH mutant-type glioma patients with and without treatment in the matched cohort, suggesting the need for further clinical studies with adequate follow-up and sample size to assess the impact of treatment on LGGs.

To the best of our knowledge, no previous study has reported on the prognosis of gliomas patients based on different biomarkers. There are some limitations in our study. First, some information, including tumour size, neurological function, symptoms, complications, physical health, socioeconomic status and recent advancements in treatment technologies such as preoperative functional MRI,[33] awake craniotomy[34] are lacking in the SEER database. The absence of this information may impact our comprehension of glioma prognosis. Second, as the data for this study were derived from existing records in the SEER database, the acquisition process of the relevant data could not be retrospectively supervised, thereby reducing the potential measurement bias. Third, a certain degree of selection bias was present in the analysis process, primarily arising from the following reasons. A portion of the population was excluded due to incomplete information (Perhaps data imputation could be used to overcome this, but it is equally contentious.). During the randomisation process, it is not always possible to create two entirely identical datasets (training and validation sets), which somewhat hinders the complete reproducibility of the analysis process. The PSM process itself results in the exclusion of some patients, and there is no universally accepted standard for setting calliper values. Finally, although this study provides a reference for prognosis and treatment of glioma patients, based on clinical practice of evidence-based medicine, further evidence is needed to prove the reliability and utility of the nomogram model.

CONCLUSION

In this study, a nomogram model was developed with strong predictive accuracy to assess different treatment options for glioma patients based on their individual characteristics. Surgery, radiotherapy and chemotherapy generally improved prognosis for glioma patients, but the choice of local aggressive treatment (surgery or radiotherapy) should be made carefully based on the patient's risk profile. For IDH wild-type glioma patients, surgery, radiotherapy or chemotherapy were viable treatment options, but for IDH mutant-type glioma patients, the appropriate treatment remains uncertain. The above findings suggest that individualised treatment for glioma patients, considering both genetic and clinical features, is necessary. Conducting future randomised controlled trials or larger real-world studies will further enhance our understanding of the results.

Contributors XL(as the guarantor): study design, acquisition of data, statistical analysis, interpretation and drawing up the first draft. JZ: conceptualisation, methodology and supervision. YS: statistical analysis and interpretation. ZW: figures and tables editing.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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ORCID iD

XinRong Li http://orcid.org/0000-0002-3188-2929

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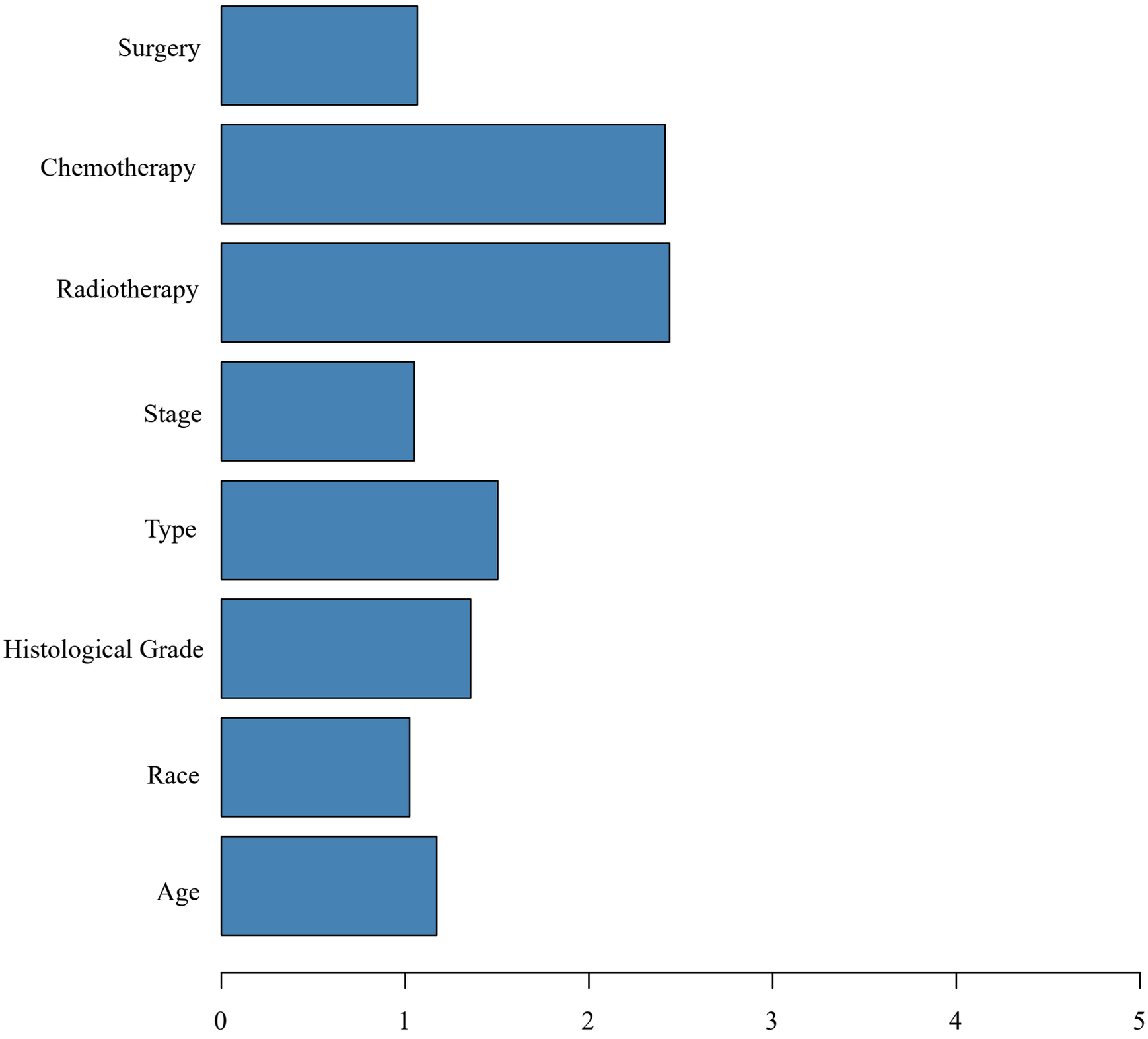
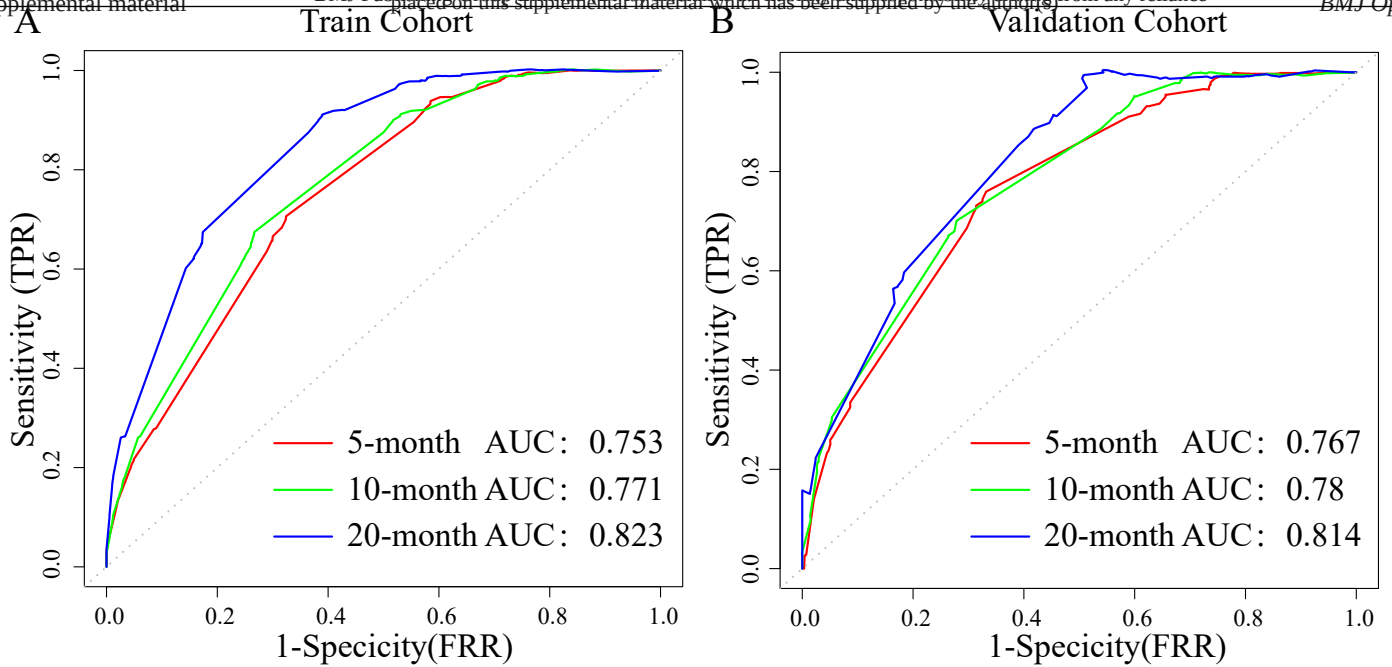
Supp Figure 1



Supp. Figure 2



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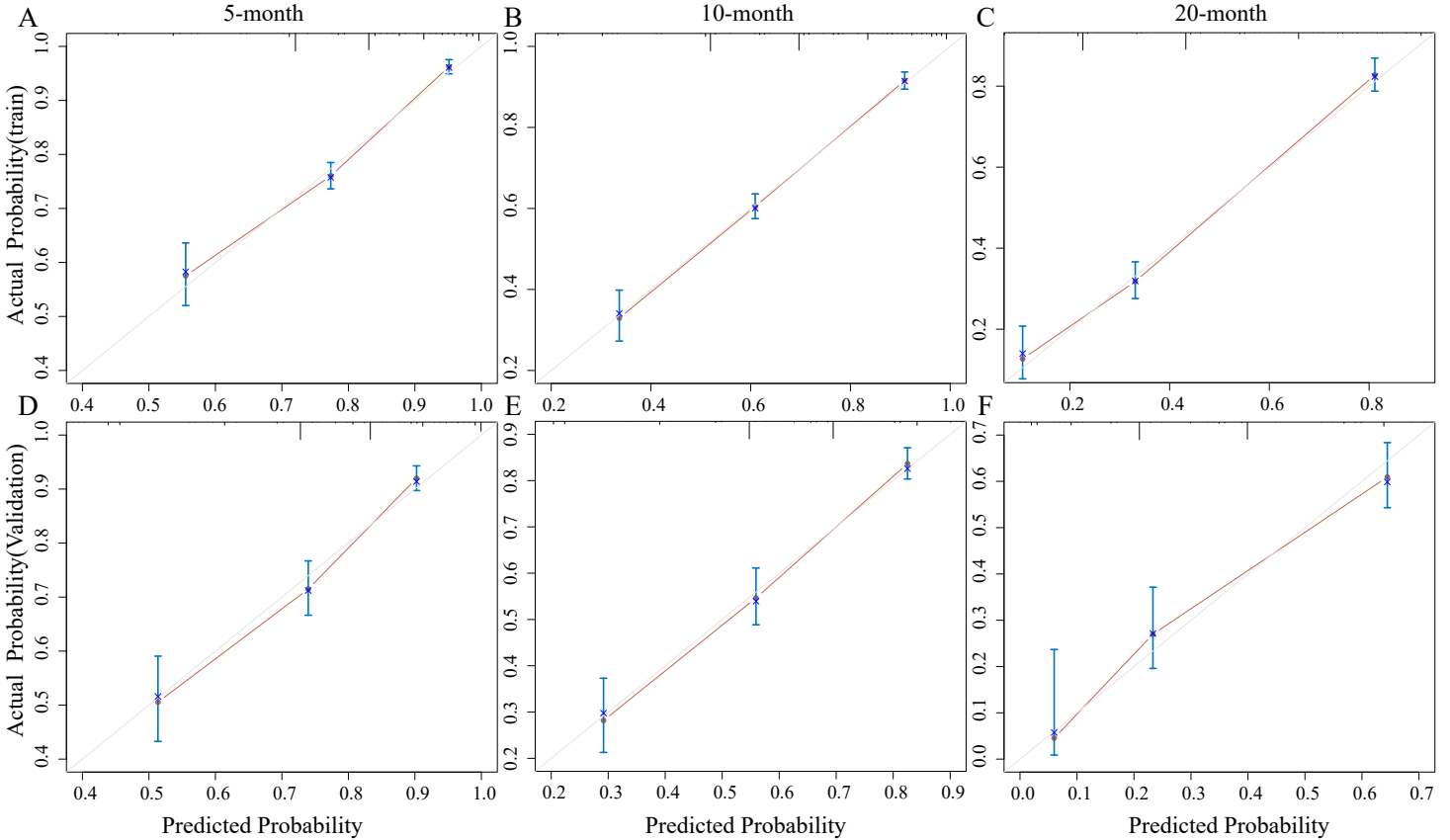

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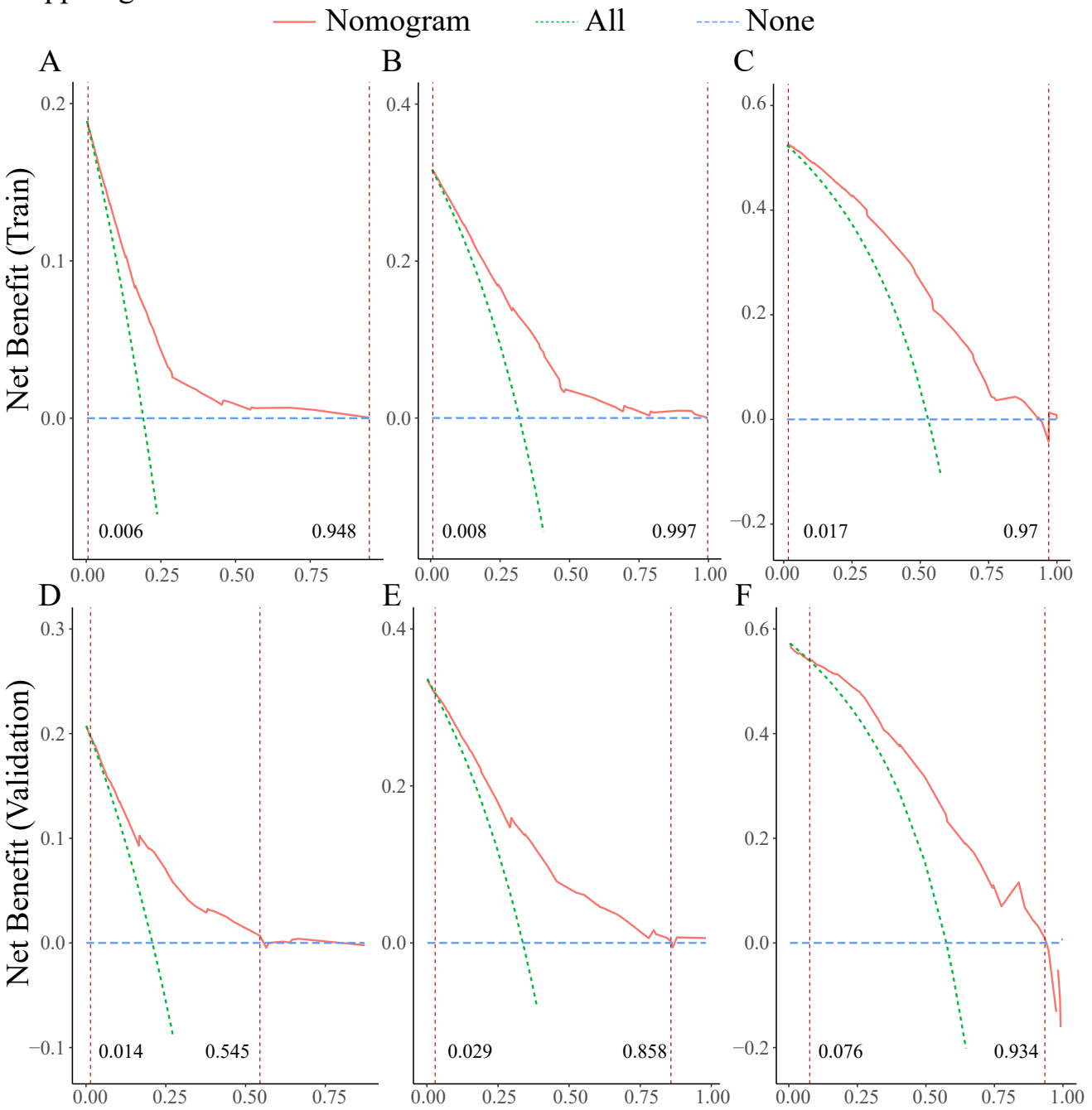

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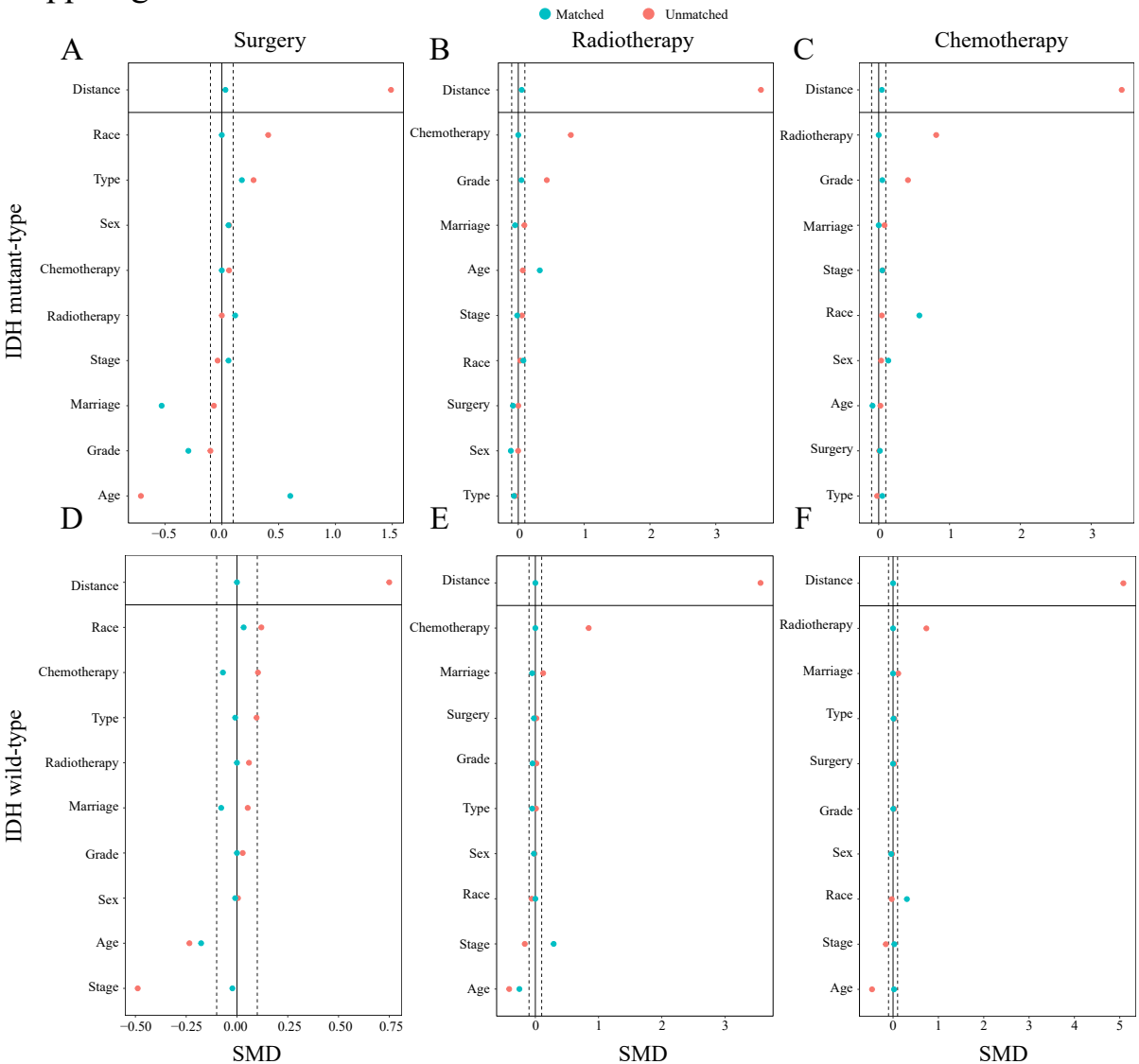

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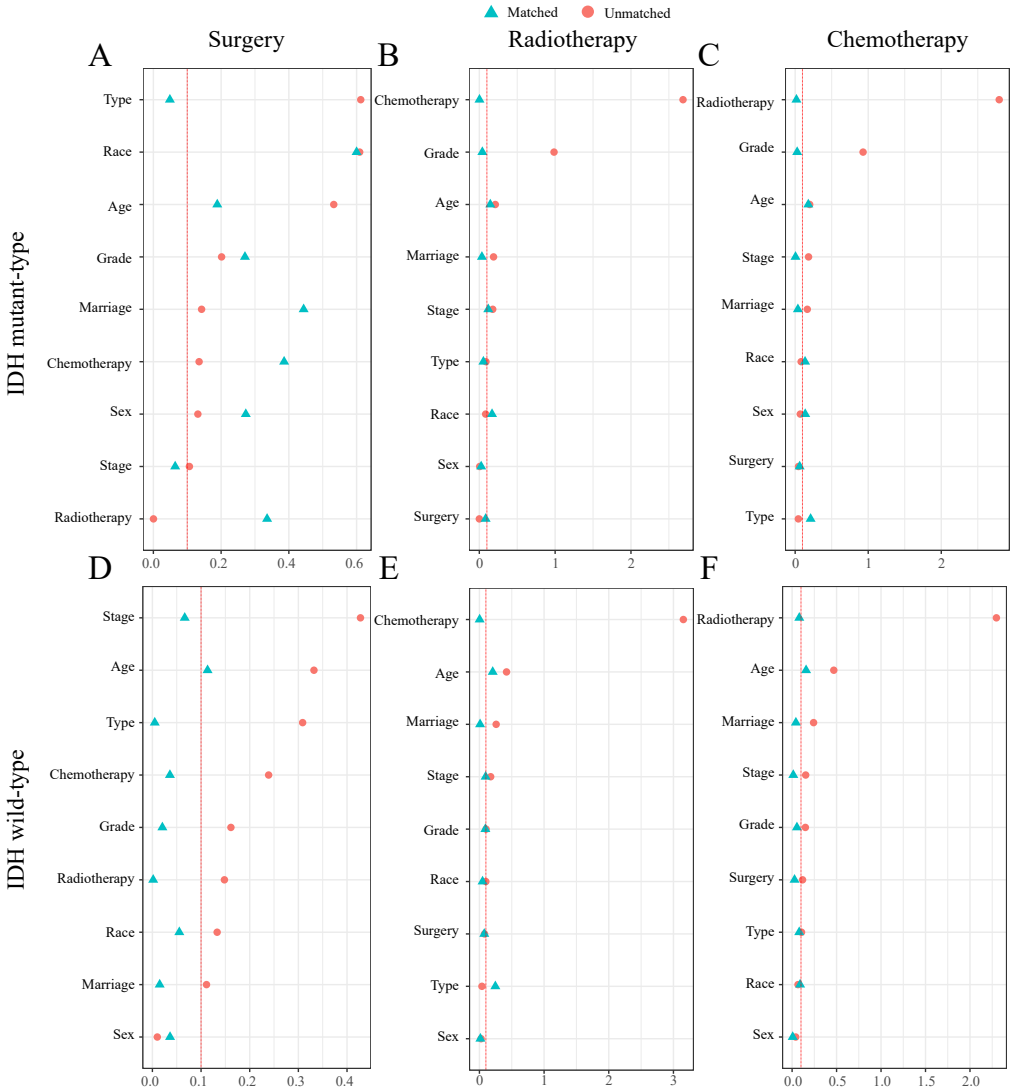

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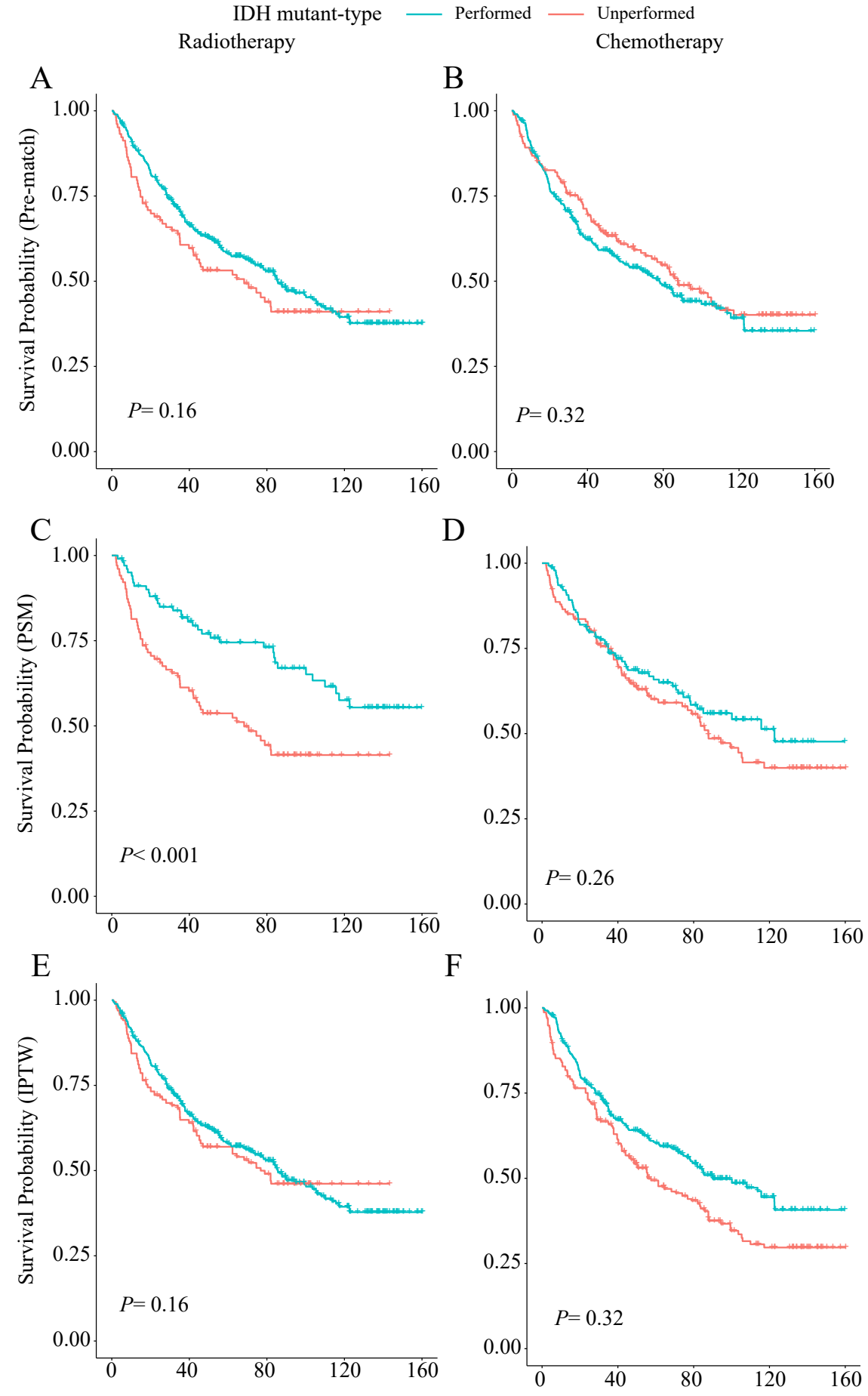
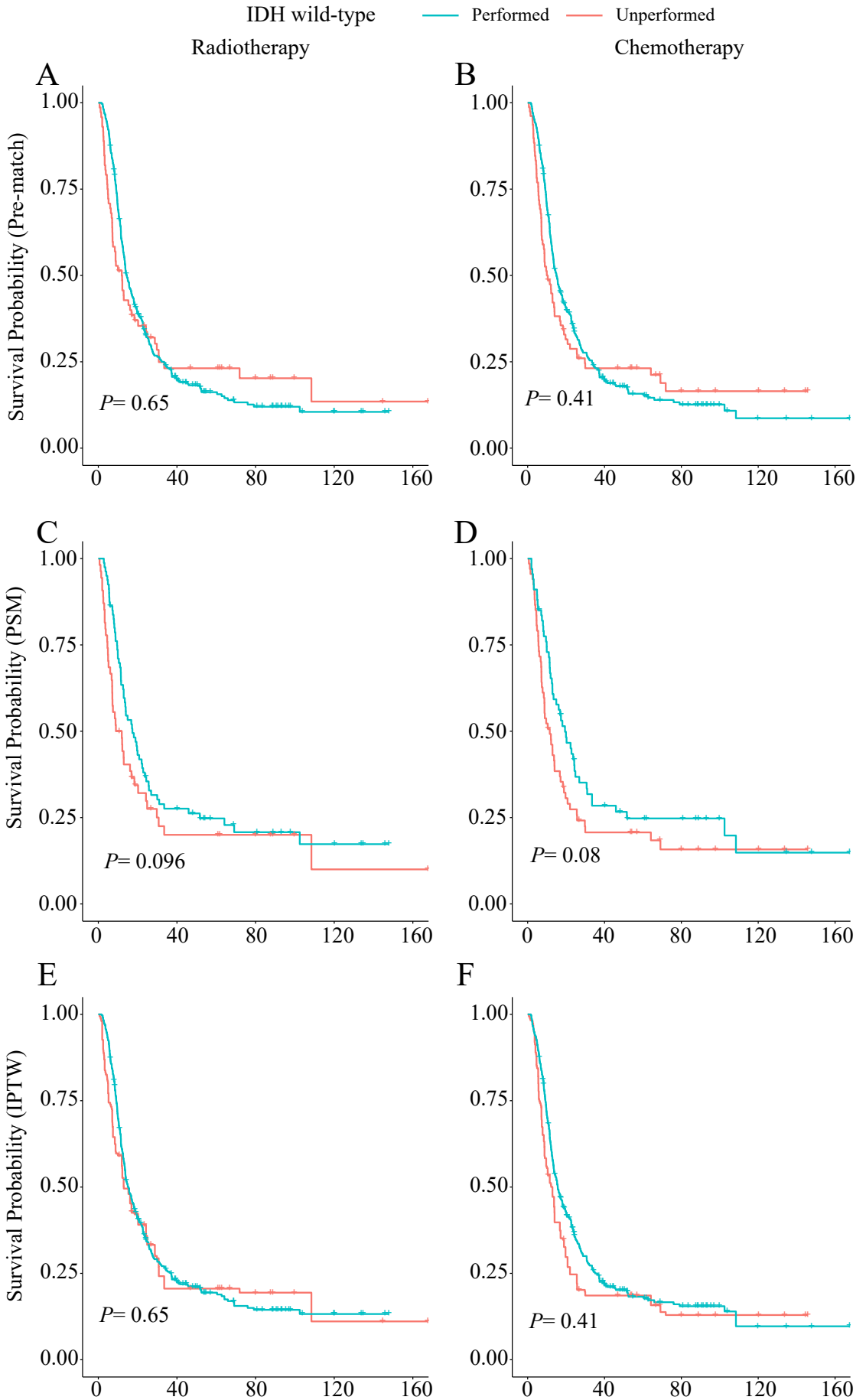


Supp. Figure 8



Supplementary Figure comments:

Supplementary Figure 1. The VIF values of the variants included in the multivariate Cox regression model. VIF: variance inflation factor.

Supplementary Figure 2. The ROC curves for the nomogram in the train (A) and validation (B) cohorts. ROC curve: receiver operating characteristic curve.

Supplementary Figure 3. The calibration curves of nomogram for predicting 5-, 10-, and 20-month survival probabilities in the train cohort (A, B, C). The calibration curves of nomogram for predicting 5-, 10-, and 20-month survival probabilities in the validation cohort (D, E, F)

Supplementary Figure 4. Decision curve analysis of the nomogram for 5-month, 10-month and 20-month overall survival in train (A, B, C) and validation (D, E, F) cohorts.

Supplementary Figure 5. SMD of characteristics before and after PSM according to different treatment and IDH status (IDH mutant-type cohorts: A-surgery, B-radiotherapy, C-chemotherapy; IDH wild-type cohorts: D-surgery, E-radiotherapy, F-chemotherapy) SMD: standardized mean difference; PSM: propensity score matching.

Supplementary Figure 6. SMD of characteristics before and after IPTW according to different treatment and IDH status (IDH mutant-type cohort: A-surgery, B-radiotherapy, C-chemotherapy; IDH wild-type cohort: D-surgery, E-radiotherapy, F-chemotherapy) SMD: standardized mean difference; IPTW: inverse probability of treatment weighting.

Supplementary Figure 7. The Kaplan-Meier survival curves of evaluating the influence of treatment on survival probability based on the pre-match (A, radiotherapy; B, chemotherapy), PSM (C, radiotherapy; D, chemotherapy) and IPTW (E, radiotherapy; F, chemotherapy;) cohorts involving IDH-mutant individuals from CGGA. PSM: propensity score matching; IPTW: inverse probability of treatment weighting.

Supplementary Figure 8. The Kaplan-Meier survival curves of evaluating the influence of treatment on survival probability based on the pre-match (A, radiotherapy; B, chemotherapy), PSM (C, radiotherapy; D, chemotherapy) and IPTW (E, radiotherapy; F, chemotherapy;) cohorts involving IDH-wild individuals from CGGA. PSM: propensity score matching; IPTW: inverse probability of treatment weighting.

Supplementary Table 1. Baseline characteristics in the whole, train and validation cohorts

Characteristics	Whole cohort	Train cohort	Validation cohort
	n= 3798	n= 2660	n= 1138
Age (%)			
18-49y	994 (26.2)	715 (26.9)	279 (24.5)
50-64y	1415 (37.3)	988 (37.1)	427 (37.5)
65-79y	1230 (32.4)	851 (32.0)	379 (33.3)
>=80y	159 (4.2)	106 (4.0)	53 (4.7)
Sex (%)			
Female	1557 (41.0)	1092 (41.1)	465 (40.9)
Male	2241 (59.0)	1568 (58.9)	673 (59.1)
Race (%)			
White	3309 (87.1)	2321 (87.3)	988 (86.8)
Black	236 (6.2)	166 (6.2)	70 (6.2)
Other races [a]	253 (6.7)	173 (6.5)	80 (7.0)
Marriage (%)			
married	2476 (65.2)	1725 (64.8)	751 (66.0)
unmarried	1322 (34.8)	935 (35.2)	387 (34.0)
Histological type [b]			
AST (IDH-wild)	390 (10.3)	286 (10.8)	104 (9.1)
AST (IDH-mutant)	210 (5.5)	150 (5.6)	60 (5.3)
OLI (IDH-mutant)	2834 (74.6)	1964 (73.8)	870 (76.4)
GBM (IDH-mutant)	364 (9.6)	260 (9.8)	104 (9.1)
Histological grade [c]			
I/II	449 (11.8)	327 (12.3)	122 (10.7)
III/IV	3349 (88.2)	2333 (87.7)	1016 (89.3)
Stage			
Localized	3257 (85.8)	2284 (85.9)	973 (85.5)
Regional	508 (13.4)	352 (13.2)	156 (13.7)

Distant	33 (0.9)	24 (0.9)	9 (0.8)
Surgery			
No	149 (3.9)	109 (4.1)	40 (3.5)
STR	3556 (93.6)	2487 (93.5)	1069 (93.9)
GTR	93 (2.4)	64 (2.4)	29 (2.5)
Radiotherapy			
No	768 (20.2)	548 (20.6)	220 (19.3)
Yes	3030 (79.8)	2112 (79.4)	918 (80.7)
Chemotherapy			
No	866 (22.8)	607 (22.8)	259 (22.8)
Yes	2932 (77.2)	2053 (77.2)	879 (77.2)

a. Other races (American Indian/AK Native, Asian/Pacific Islander);
b. AST: astrocytoma; OLI: oligodendroglioma, 1 p/19q co-deleted; GBM: glioblastoma; IDH: isocitrate dehydrogenase;
c. I, WHO Grade I; II, WHO Grade II; III, WHO Grade III; IV, WHO Grade IV

Supplementary Table 2. Clinical characteristics before and after IPTW/PSM according to surgery or not in IDH [a] wild-type cohort

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No	Yes		No	Yes		No	Yes	
	n= 130	n= 2914		Value= 2985.2	Value= 3044.5		n= 116	n= 116	
Age (%)									
18-49y	19 (14.6)	421 (14.4)	0.003	532.3 (17.8)	440.3 (14.5)	0.708	11 (9.5)	8 (6.9)	0.679
50-64y	36 (27.7)	1223 (42.0)		1113.1 (37.3)	1258.7 (41.3)		16 (13.8)	21 (18.1)	
65-79y	63 (48.5)	1128 (38.7)		1160.2 (38.9)	1190.9 (39.1)		30 (25.9)	33 (28.4)	
>=80y	12 (9.2)	142 (4.9)		179.7 (6.0)	154.7 (5.1)		59 (50.9)	54 (46.6)	
Sex (%)									
Female	52 (40.0)	1180 (40.5)	0.983	1261.7 (42.3)	1232.4 (40.5)	0.734	45 (38.8)	44 (37.9)	>0.999
Male	78 (60.0)	1734 (59.5)		1723.5 (57.7)	1812.2 (59.5)		71 (61.2)	72 (62.1)	
Race (%)									
White	119 (91.5)	2551 (87.5)	0.389	2583.3 (86.5)	2670.4 (87.7)	0.9	108 (93.1)	107 (92.2)	0.953
Black	6 (4.6)	184 (6.3)		180.2 (6.0)	190.1 (6.2)		3 (2.6)	3 (2.6)	
Other [c]	5 (3.8)	179 (6.1)		221.7 (7.4)	184.0 (6.0)		5 (4.3)	6 (5.2)	
Marriage (%)									
Unmarried	49 (37.7)	944 (32.4)	0.244	995.3 (33.3)	993.6 (32.6)	0.883	42 (36.2)	51 (44.0)	0.284
Married	81 (62.3)	1970 (67.6)		1989.9 (66.7)	2050.9 (67.4)		74 (63.8)	65 (56.0)	
Histological type [d] (%)									
Astrocytoma	21 (16.2)	189 (6.5)	<0.001	202.6 (6.8)	210.3 (6.9)	0.946	10 (8.6)	11 (9.5)	>0.999
Glioblastoma	109 (83.8)	2725 (93.5)		2782.6 (93.2)	2834.2 (93.1)		106 (91.4)	105 (90.5)	
Histological grade [e] (%)									
I/II	6 (4.6)	52 (1.8)	0.047	48.7 (1.6)	57.8 (1.9)	0.77	1 (0.9)	1 (0.9)	>0.999
III/IV	124 (95.4)	2862 (98.2)		2936.6 (98.4)	2986.7 (98.1)		115 (99.1)	115 (99.1)	

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No	Yes		No	Yes		No	Yes	
	n= 130	n= 2914		Value= 2985.2	Value= 3044.5		n= 116	n= 116	
Stage (%)									
Localized	89 (68.5)	2506 (86.0)	<0.001	2475.8 (82.9)	2594.5 (85.2)	0.658	81 (69.8)	82 (70.7)	0.99
Regional	38 (29.2)	378 (13.0)		479.2 (16.1)	416.9 (13.7)		34 (29.3)	33 (28.4)	
Distant	3 (2.3)	30 (1.0)		30.3 (1.0)	33.1 (1.1)		1 (0.9)	1 (0.9)	
Radiotherapy (%)									
No	30 (23.1)	500 (17.2)	0.105	518.0 (17.4)	530.2 (17.4)	0.986	27 (23.3)	27 (23.3)	>0.999
Yes	100 (76.9)	2414 (82.8)		2467.3 (82.6)	2514.4 (82.6)		89 (76.7)	89 (76.7)	
Chemotherapy (%)									
No	40 (30.8)	595 (20.4)	0.006	580.0 (19.4)	635.5 (20.9)	0.689	32 (27.6)	40 (34.5)	0.321
Yes	90 (69.2)	2319 (79.6)		2405.2 (80.6)	2409.0 (79.1)		84 (72.4)	76 (65.5)	

a. IDH, Isocitrate Dehydrogenase;

b. The *P* value calculated with the use of a chi-square test;

c. Other races (American Indian/AK Native, Asian/Pacific Islander);

d. Astrocytoma (IDH wild-type without 1 p/19q co-deleted), Glioblastoma (IDH wild-type without 1 p/19q co-deleted)

e. I, WHO Grade I; II, WHO Grade II; III, WHO Grade III; IV, WHO Grade IV

Supplementary Table 3. Clinical characteristics before and after IPTW/PSM according to radiotherapy or not in IDH [a] wild-type cohort

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No	Yes		No	Yes		No	Yes	
	n= 530	n= 2514		Value= 3054.3	Value= 3047		n= 180	n= 180	
Age (%)									
18-49y	47 (8.9)	393 (15.6)	<0.001	407.0 (13.3)	439.6 (14.4)	0.42	14 (7.8)	31 (17.2)	0.054

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No	Yes		No	Yes		No	Yes	
	n= 530	n= 2514		Value= 3054.3	Value= 3047		n= 180	n= 180	
50-64y	173 (32.6)	1086 (43.2)		1098.9 (36.0)	1246.3 (40.9)		56 (31.1)	52 (28.9)	
65-79y	249 (47.0)	942 (37.5)		1222.2 (40.0)	1196.0 (39.3)		89 (49.4)	81 (45.0)	
>=80y	61 (11.5)	93 (3.7)		326.3 (10.7)	165.0 (5.4)		21 (11.7)	16 (8.9)	
Sex (%)									
Female	220 (41.5)	1012 (40.3)	0.627	1257.5 (41.2)	1231.6 (40.4)	0.902	64 (35.6)	60 (33.3)	0.739
Male	310 (58.5)	1502 (59.7)		1796.8 (58.8)	1815.3 (59.6)		116 (64.4)	120 (66.7)	
Race (%)									
White	453 (85.5)	2217 (88.2)	0.092	2674.9 (87.6)	2667.4 (87.5)	0.891	160 (88.9)	160 (88.9)	>0.999
Black	44 (8.3)	146 (5.8)		222.8 (7.3)	196.8 (6.5)		13 (7.2)	13 (7.2)	
Other [c]	33 (6.2)	151 (6.0)		156.6 (5.1)	182.7 (6.0)		7 (3.9)	7 (3.9)	
Marriage (%)									
Unmarried	227 (42.8)	766 (30.5)	<0.001	993.3 (32.5)	1005.9 (33.0)	0.925	67 (37.2)	76 (42.2)	0.389
Married	303 (57.2)	1748 (69.5)		2061.0 (67.5)	2041.1 (67.0)		113 (62.8)	104 (57.8)	
Histological type [d] (%)									
Astrocytoma	41 (7.7)	169 (6.7)	0.458	454.3 (14.9)	219.7 (7.2)	0.046	15 (8.3)	24 (13.3)	0.175
Glioblastoma	489 (92.3)	2345 (93.3)		2600.1 (85.1)	2827.3 (92.8)		165 (91.7)	156 (86.7)	
Histological grade [e] (%)									
I/II	17 (3.2)	41 (1.6)	0.025	25.0 (0.8)	57.3 (1.9)	0.008	1 (0.6)	9 (5.0)	0.025
III/IV	513 (96.8)	2473 (98.4)		3029.4 (99.2)	2989.7 (98.1)		179 (99.4)	171 (95.0)	
Stage (%)									
Localized	424 (80.0)	2171 (86.4)	0.001	2660.3 (87.1)	2604.3 (85.5)	0.402	158 (87.8)	140 (77.8)	0.039
Regional	100 (18.9)	316 (12.6)		384.6 (12.6)	410.3 (13.5)		21 (11.7)	37 (20.6)	
Distant	6 (1.1)	27 (1.1)		9.4 (0.3)	32.3 (1.1)		1 (0.6)	3 (1.7)	

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No n= 530	Yes n= 2514		No Value= 3054.3	Yes Value= 3047		No n= 180	Yes n= 180	
Chemotherapy (%)									
No	480 (90.6)	155 (6.2)	<0.001	635.2 (20.8)	638.0 (20.9)	0.961	130 (72.2)	130 (72.2)	>0.999
Yes	50 (9.4)	2359 (93.8)		2419.2 (79.2)	2409.0 (79.1)		50 (27.8)	50 (27.8)	
Surgery (%)									
No	30 (5.7)	100 (4.0)	0.105	183.2 (6.0)	132.2 (4.3)	0.567	5 (2.8)	9 (5.0)	0.413
Yes	500 (94.3)	2414 (96.0)		2871.2 (94.0)	2914.8 (95.7)		175 (97.2)	171 (95.0)	

a. IDH, Isocitrate Dehydrogenase;

b. The *P* value calculated with the use of a chi-square test;

c. Other races (American Indian/AK Native, Asian/Pacific Islander);

d. Astrocytoma (IDH wild-type without 1 p/19q co-deleted), Glioblastoma (IDH wild-type without 1 p/19q co-deleted)

e. I, WHO Grade I; II, WHO Grade II; III, WHO Grade III; IV, WHO Grade IV

Supplementary Table 4. Clinical characteristics before and after IPTW/PSM according to chemotherapy or not in IDH [a] wild-type cohort

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No n= 530	Yes n= 2514		No Value= 3054.3	Yes Value= 3047		No n= 180	Yes n= 180	
Age (%)									
18-49y	55 (8.7)	385 (16.0)	<0.001	426.8 (14.5)	433.9 (13.6)	0.374	15 (8.2)	15 (8.2)	0.995
50-64y	200 (31.5)	1059 (44.0)		1143.4 (38.7)	1220.9 (38.3)		57 (31.1)	55 (30.1)	
65-79y	306 (48.2)	885 (36.7)		1217.4 (41.2)	1225.9 (38.5)		94 (51.4)	95 (51.9)	
>=80y	74 (11.7)	80 (3.3)		163.7 (5.5)	307.5 (9.6)		17 (9.3)	18 (9.8)	
Sex (%)									

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No n= 530	Yes n= 2514		No Value= 3054.3	Yes Value= 3047		No n= 180	Yes n= 180	
Female	267 (42.0)	965 (40.1)	0.388	1131.6 (38.3)	1233.0 (38.7)	0.935	72 (39.3)	65 (35.5)	0.517
Male	368 (58.0)	1444 (59.9)		1819.7 (61.7)	1955.1 (61.3)		111 (60.7)	118 (64.5)	
Race (%)									
White	549 (86.5)	2121 (88.0)	0.304	2519.6 (85.4)	2810.7 (88.2)	0.542	160 (87.4)	136 (74.3)	0.004
Black	48 (7.6)	142 (5.9)		251.8 (8.5)	201.3 (6.3)		13 (7.1)	32 (17.5)	
Other [c]	38 (6.0)	146 (6.1)		179.9 (6.1)	176.1 (5.5)		10 (5.5)	15 (8.2)	
Marriage (%)									
Unmarried	265 (41.7)	728 (30.2)	<0.001	980.3 (33.2)	1123.5 (35.2)	0.619	65 (35.5)	65 (35.5)	>0.999
Married	370 (58.3)	1681 (69.8)		1971.0 (66.8)	2064.7 (64.8)		118 (64.5)	118 (64.5)	
Histological type [d] (%)									
Astrocytoma	58 (9.1)	152 (6.3)	0.016	239.2 (8.1)	332.5 (10.4)	0.413	16 (8.7)	14 (7.7)	0.849
Glioblastoma	577 (90.9)	2257 (93.7)		2712.1 (91.9)	2855.7 (89.6)		167 (91.3)	169 (92.3)	
Histological grade [e] (%)									
I/II	24 (3.8)	34 (1.4)	<0.001	58.9 (2.0)	41.6 (1.3)	0.235	2 (1.1)	1 (0.5)	>0.999
III/IV	611 (96.2)	2375 (98.6)		2892.4 (98.0)	3146.6 (98.7)		181 (98.9)	182 (99.5)	
Stage (%)									
Localized	513 (80.8)	2082 (86.4)	0.002	2520.5 (85.4)	2736.5 (85.8)	0.962	159 (86.9)	157 (85.8)	0.951
Regional	113 (17.8)	303 (12.6)		406.6 (13.8)	424.7 (13.3)		22 (12.0)	24 (13.1)	
Distant	9 (1.4)	24 (1.0)		24.2 (0.8)	27.0 (0.8)		2 (1.1)	2 (1.1)	
Radiotherapy (%)									
No	480 (75.6)	50 (2.1)	<0.001	530.7 (18.0)	675.7 (21.2)	0.322	39 (21.3)	39 (21.3)	>0.999
Yes	155 (24.4)	2359 (97.9)		2420.6 (82.0)	2512.5 (78.8)		144 (78.7)	144 (78.7)	
Surgery (%)									

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No	Yes		No	Yes		No	Yes	
	n= 530	n= 2514		Value= 3054.3	Value= 3047		n= 180	n= 180	
No	40 (6.3)	90 (3.7)	0.006	113.9 (3.9)	140.5 (4.4)	0.706	6 (3.3)	6 (3.3)	>0.999
Yes	595 (93.7)	2319 (96.3)		2837.4 (96.1)	3047.7 (95.6)		177 (96.7)	177 (96.7)	

a. IDH, Isocitrate Dehydrogenase;

b. The *P* value calculated with the use of a chi-square test;

c. Other races (American Indian/AK Native, Asian/Pacific Islander);

d. Astrocytoma (IDH wild-type without 1 p/19q co-deleted), Glioblastoma (IDH wild-type without 1 p/19q co-deleted);

e. I, WHO Grade I; II, WHO Grade II; III, WHO Grade III; IV, WHO Grade IV

Supplementary Table5. Clinical characteristics before and after IPTW/PSM according to surgery or not in IDH [a] mutant-type cohort

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No	Yes		No	Yes		No	Yes	
	n= 19	n= 735		Value= 602.1	Value= 753.9		n= 17	n= 17	
Age (%)									
18-49y	11 (57.9)	543 (73.9)	<0.001	390.2 (64.8)	553.9 (73.5)	0.754	11 (64.7)	7 (41.2)	0.376
50-64y	4 (21.1)	152 (20.7)		166.2 (27.6)	156.1 (20.7)		4 (23.5)	6 (35.3)	
65-79y	2 (10.5)	37 (5.0)		41.0 (6.8)	39.1 (5.2)		2 (11.8)	4 (23.5)	
>=80y	2 (10.5)	3 (0.4)		4.7 (0.8)	4.9 (0.6)				
Sex (%)									
Female	7 (36.8)	318 (43.3)	0.746	341.5 (56.7)	325.7 (43.2)	0.344	7 (41.2)	8 (47.1)	>0.999
Male	12 (63.2)	417 (56.7)		260.6 (43.3)	428.2 (56.8)		10 (58.8)	9 (52.9)	
Race (%)									
White	19 (100.0)	620 (84.4)	0.173	602.1 (100.0)	638.9 (84.7)	<0.001	17 (100.0)	17 (100.0)	-

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No n= 19	Yes n= 735		No Value= 602.1	Yes Value= 753.9		No n= 17	Yes n= 17	
Black	0 (0.0)	46 (6.3)		0.0 (0.0)	46.0 (6.1)				
Other [c]	0 (0.0)	69 (9.4)		0.0 (0.0)	69.0 (9.2)				
Marriage (%)									
Unmarried	7 (36.8)	322 (43.8)	0.711	139.5 (23.2)	328.7 (43.6)	0.089	6 (35.3)	15 (88.2)	0.005
Married	12 (63.2)	413 (56.2)		462.6 (76.8)	425.3 (56.4)		11 (64.7)	2 (11.8)	
Histological type [d] (%)									
Astrocytoma	15 (78.9)	375 (51.0)	0.03	326.1 (54.2)	389.9 (51.7)	0.878	13 (76.5)	10 (58.8)	0.463
Oligodendroglioma	4 (21.1)	360 (49.0)		276.1 (45.8)	364.0 (48.3)		4 (23.5)	7 (41.2)	
Histological grade [e] (%)									
I/II	8 (42.1)	383 (52.1)	0.529	391.9 (65.1)	391.1 (51.9)	0.319	8 (47.1)	13 (76.5)	0.158
III/IV	11 (57.9)	352 (47.9)		210.2 (34.9)	362.8 (48.1)		9 (52.9)	4 (23.5)	
Stage (%)									
Localized	16 (84.2)	646 (87.9)	0.897	540.7 (89.8)	661.7 (87.8)	0.774	14 (82.4)	13 (76.5)	>0.999
Regional	3 (15.8)	89 (12.1)		61.5 (10.2)	92.3 (12.2)		3 (17.6)	4 (23.5)	
Radiotherapy (%)									
No	6 (31.6)	232 (31.6)	>0.999	288.3 (47.9)	238.8 (31.7)	0.263	6 (35.3)	4 (23.5)	0.707
Yes	13 (68.4)	503 (68.4)		313.8 (52.1)	515.2 (68.3)		11 (64.7)	13 (76.5)	
Chemotherapy (%)									
No	7 (36.8)	224 (30.5)	0.732	296.9 (49.3)	231.8 (30.7)	0.194	7 (41.2)	7 (41.2)	>0.999
Yes	12 (63.2)	511 (69.5)		305.2 (50.7)	522.2 (69.3)		10 (58.8)	10 (58.8)	

a. IDH, Isocitrate Dehydrogenase;

b. The *P* value calculated with the use of a chi-square test;

c. Other races (American Indian/AK Native, Asian/Pacific Islander);

d. Astrocytoma (IDH mutant-type without 1 p/19q co-deleted), Oligodendroglioma (IDH mutant-type with 1 p/19q co-deleted)
e. I, WHO Grade I; II, WHO Grade II; III, WHO Grade III; IV, WHO Grade IV

Supplementary Table 6. Clinical characteristics before and after IPTW/PSM according to radiotherapy or not in IDH [a] mutant-type cohort

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No	Yes		No	Yes		No	Yes	
	n= 238	n= 516		Value= 768.8	Value= 748.5		n= 62	n= 62	
Age (%)									
18-49y	185 (77.7)	369 (71.5)	0.065	530.8 (69.0)	532.8 (71.2)	0.53	41 (66.1)	34 (54.8)	0.391
50-64y	37 (15.5)	119 (23.1)		219.3 (28.5)	183.1 (24.5)		19 (30.6)	22 (35.5)	
65-79y	13 (5.5)	26 (5.0)		15.5 (2.0)	30.3 (4.0)		1 (1.6)	4 (6.5)	
>=80y	3 (1.3)	2 (0.4)		3.2 (0.4)	2.2 (0.3)		1 (1.6)	2 (3.2)	
Sex (%)									
Female	103 (43.3)	222 (43.0)	>0.999	363.7 (47.3)	344.8 (46.1)	0.883	29 (46.8)	22 (35.5)	0.274
Male	135 (56.7)	294 (57.0)		405.2 (52.7)	403.6 (53.9)		33 (53.2)	40 (64.5)	
Race (%)									
White	202 (84.9)	437 (84.7)	0.566	609.3 (79.2)	627.4 (83.8)	0.613	50 (80.6)	47 (75.8)	0.675
Black	17 (7.1)	29 (5.6)		87.1 (11.3)	49.1 (6.6)		5 (8.1)	8 (12.9)	
Other [c]	19 (8.0)	50 (9.7)		72.5 (9.4)	71.9 (9.6)		7 (11.3)	7 (11.3)	
Marriage (%)									
Unmarried	119 (50.0)	210 (40.7)	0.021	323.8 (42.1)	327.9 (43.8)		30 (48.4)	33 (53.2)	0.719
Married	119 (50.0)	306 (59.3)		445.0 (57.9)	420.5 (56.2)	0.832	32 (51.6)	29 (46.8)	
Histological type [d] (%)									
Astrocytoma	116 (48.7)	274 (53.1)	0.3	354.4 (46.1)	365.1 (48.8)	0.751	25 (40.3)	29 (46.8)	0.587
Oligodendroglioma	122 (51.3)	242 (46.9)		414.4 (53.9)	383.3 (51.2)		37 (59.7)	33 (53.2)	

Histological grade [e] (%)									
I/II	194 (81.5)	197 (38.2)	<0.001	375.7 (48.9)	380.8 (50.9)	0.809	40 (64.5)	37 (59.7)	0.711
III/IV	44 (18.5)	319 (61.8)		393.1 (51.1)	367.7 (49.1)		22 (35.5)	25 (40.3)	
Stage (%)									
Localized	218 (91.6)	444 (86.0)	0.041	687.1 (89.4)	639.6 (85.5)	0.439	54 (87.1)	55 (88.7)	>0.999
Regional	20 (8.4)	72 (14.0)		81.7 (10.6)	108.8 (14.5)		8 (12.9)	7 (11.3)	
Chemotherapy (%)									
No	203 (85.3)	28 (5.4)	<0.001	230.7 (30.0)	225.3 (30.1)	0.987	27 (43.5)	27 (43.5)	>0.999
Yes	35 (14.7)	488 (94.6)		538.2 (70.0)	523.1 (69.9)		35 (56.5)	35 (56.5)	
Surgery (%)									
No	6 (2.5)	13 (2.5)	>0.999	7.4 (1.0)	14.7 (2.0)	0.163	2 (3.2)	7 (11.3)	0.166
Yes	232 (97.5)	503 (97.5)		761.4 (99.0)	733.8 (98.0)		60 (96.8)	55 (88.7)	

a. IDH, Isocitrate Dehydrogenase;

b. The *P* value calculated with the use of a chi-square test;

c. Other races (American Indian/AK Native, Asian/Pacific Islander);

d. Astrocytoma (IDH mutant-type without 1 p/19q co-deleted), Oligodendroglioma (IDH mutant-type with 1 p/19q co-deleted)

e. I, WHO Grade I; II, WHO Grade II; III, WHO Grade III; IV, WHO Grade IV

Supplementary Table 7. Clinical characteristics before and after IPTW/PSM according to chemotherapy or not in IDH [a] mutant-type cohort

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No	Yes		No	Yes		No	Yes	
	n= 231	n= 523		Value= 842.6	Value= 726.1		n= 59	n= 59	
Age (%)									
18-49y	177 (76.6)	377 (72.1)	0.09	525.5 (62.4)	513.4 (70.7)	0.521	36 (61.0)	39 (66.1)	0.839
50-64y	37 (16.0)	119 (22.8)		278.1 (33.0)	182.6 (25.2)		21 (35.6)	18 (30.5)	

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No n= 231	Yes n= 523		No Value= 842.6	Yes Value= 726.1		No n= 59	Yes n= 59	
65-79y	14 (6.1)	25 (4.8)		35.4 (4.2)	27.5 (3.8)		2 (3.4)	2 (3.4)	
>=80y	3 (1.3)	2 (0.4)		3.5 (0.4)	2.5 (0.3)				
Sex (%)									
Female	94 (40.7)	231 (44.2)	0.419	435.2 (51.7)	325.2 (44.8)	0.398	29 (49.2)	37 (62.7)	0.194
Male	137 (59.3)	292 (55.8)		407.4 (48.3)	400.9 (55.2)		30 (50.8)	22 (37.3)	
Race (%)									
White	197 (85.3)	442 (84.5)	0.59	668.0 (79.3)	609.8 (84.0)	0.709	51 (86.4)	40 (67.8)	0.03
Black	16 (6.9)	30 (5.7)		86.9 (10.3)	49.7 (6.8)		4 (6.8)	5 (8.5)	
Other [c]	18 (7.8)	51 (9.8)		87.7 (10.4)	66.7 (9.2)		4 (6.8)	14 (23.7)	
Marriage (%)									
Unmarried	114 (49.4)	215 (41.1)	0.043	393.9 (46.7)	325.9 (44.9)	0.821	28 (47.5)	28 (47.5)	>0.999
Married	117 (50.6)	308 (58.9)		448.7 (53.3)	400.2 (55.1)		31 (52.5)	31 (52.5)	
Histological type [d] (%)									
Astrocytoma	116 (50.2)	274 (52.4)	0.637	325.3 (38.6)	356.1 (49.0)	0.181	23 (39.0)	20 (33.9)	0.702
Oligodendroglioma	115 (49.8)	249 (47.6)		517.3 (61.4)	370.0 (51.0)		36 (61.0)	39 (66.1)	
Histological grade [e] (%)									
I/II	186 (80.5)	205 (39.2)	<0.001	412.4 (48.9)	365.4 (50.3)	0.865	37 (62.7)	34 (57.6)	0.707
III/IV	45 (19.5)	318 (60.8)		430.2 (51.1)	360.7 (49.7)		22 (37.3)	25 (42.4)	
Stage (%)									
Localized	212 (91.8)	450 (86.0)	0.036	732.5 (86.9)	632.4 (87.1)	0.976	51 (86.4)	48 (81.4)	0.616
Regional	19 (8.2)	73 (14.0)		110.1 (13.1)	93.7 (12.9)		8 (13.6)	11 (18.6)	
Radiotherapy (%)									
No	203 (87.9)	35 (6.7)	<0.001	236.6 (28.1)	209.7 (28.9)	0.893	31 (52.5)	31 (52.5)	>0.999

Characteristics	Pre-match Cohort		*P* [b]	IPTW Cohort		*P*	PSM Cohort		*P*
	No n= 231	Yes n= 523		No Value= 842.6	Yes Value= 726.1		No n= 59	Yes n= 59	
Yes	28 (12.1)	488 (93.3)		606.0 (71.9)	516.4 (71.1)		28 (47.5)	28 (47.5)	
Surgery (%)									
No	7 (3.0)	12 (2.3)	0.732	23.7 (2.8)	13.7 (1.9)	0.606	1 (1.7)	0 (0.0)	>0.999
Yes	224 (97.0)	511 (97.7)		818.9 (97.2)	712.4 (98.1)		58 (98.3)	59 (100.0)	

a. IDH, Isocitrate Dehydrogenase;

b. The *P* value calculated with the use of a chi-square test;

c. Other races (American Indian/AK Native, Asian/Pacific Islander);

d. Astrocytoma (IDH mutant-type without 1 p/19q co-deleted), Oligodendroglioma (IDH mutant-type with 1 p/19q co-deleted)

e. I, WHO Grade I; II, WHO Grade II; III, WHO Grade III; IV, WHO Grade IV

Supplementary Table 8. Univariate and multivariate Cox regression analyses on overall survival in the CGGA cohort

Characteristics	Univariate analysis			Multivariate analysis		
	HR[a]	95%CI[b]	P	HR	95%CI	P
Age						
18-49y	1(Ref)					
50-64y	1.93	(1.6-2.32)	<0.001	1.09	(0.89-1.33)	0.39
65-79y	2.94	(2.06-4.19)	<0.001	1.16	(0.8-1.69)	0.43
Sex						

Characteristics	Univariate analysis			Multivariate analysis		
	HR[a]	95%CI[b]	P	HR	95%CI	P
Female	1(Ref)					
Male	1.03	(0.87-1.22)	0.74			
Histological typed [c]						
AST	1(Ref)					
OLI	0.23	(0.15-0.36)	<0.001	0.41	(0.25-0.68)	<0.001
GBM	3.49	(2.91-4.17)	<0.001			
Histological grade [d]						
II	1(Ref)					
III	3.1	(2.36-4.06)	<0.001	2.64	(1.95-3.57)	<0.001
IV	8.54	(6.55-11.13)	<0.001	5.78	(4.2-7.96)	<0.001
IDH status [e]						
Wild	1(Ref)					
Mutant	0.31	(0.26-0.37)	<0.001	0.57	(0.46-0.7)	<0.001
Radiotherapy						
No	1(Ref)					

Characteristics	Univariate analysis			Multivariate analysis		
	HR[a]	95%CI[b]	P	HR	95%CI	P
Yes	0.93	(0.76-1.15)	0.51	0.8	(0.64-0.99)	0.04
Chemotherapy						
No	1(Ref)					
Yes	1.28	(1.06-1.55)	0.01	0.63	(0.51-0.78)	<0.001

a. HR, hazard ratio; b. CI, confidence interval; c. AST, astrocytoma; OLI, oligodendroglioma, GBM, glioblastoma; d. II, WHO Grade II; III, WHO Grade III; IV, WHO Grade IV; e. IDH, isocitrate dehydrogenase.