

# A Bioinformatic Analysis: The Overexpression and Prognostic Potential of *GPX7* in Lower-Grade Glioma

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**Purpose:** Glutathione peroxidase-7 (*GPX7*) is a newly discovered non-selenium-containing protein with glutathione peroxidase activity, which mainly protects the organism from oxidative damage and is very important for basic biology studies. This study aims to reveal the expression pattern of *GPX7* and its prognosis potential from a pan-cancer perspective.

**Methods:** Expression levels of *GPX7* in human tumor tissues and normal tissues were evaluated using Human Protein Atlas (HPA), the Cancer Genome Atlas (TCGA), Genotype-Tissue Expression (GTEx) and UALCAN databases. The prognostic potential of *GPX7* for 33 TCGA tumors was evaluated by Kaplan–Meier analysis and Cox regression analysis. Subsequently, the Chinese Glioma Genome Atlas (CGGA) dataset was used to further verify the expression of *GPX7* and its prognostic potential in glioma. We explored the correlation between *GPX7* and immune infiltration, tumor mutational burden (TMB) and microsatellite instability (MSI). Furthermore, a nomogram lower-grade glioma (LGG) was constructed to verify the prognostic outcome of patients. Finally, the relationship between *GPX7* and treatment regimens for LGG was also explored.

**Results:** *GPX7* was overexpressed in multiple tumors. Elevated expression of *GPX7* was associated with poor prognosis of LGG patients (OS hazard ratio (HR) = 1.044,  $P < 0.0001$ ; DFS HR = 1.035,  $P < 0.0001$ ; PFS HR = 1.045,  $P < 0.0001$ ). *GPX7* was proved to be an independent prognostic factor of LGG through univariate and multivariate Cox analysis. The nomogram confirmed a better predictability (Concordance index (C-index): 0.845; 95% CI, 0.825–0.865). *GPX7* was positively correlated with TMB in LGG. *GPX7* expression was negatively correlated with half-maximal inhibitory concentration (IC50) of temozolomide (TMZ) ( $\rho_{\text{spearman}} = -0.59$ ,  $P = 1.3e-48$ ).

**Conclusion:** *GPX7* was upregulated in multiple tumors, and it was a potential prognostic biomarker in LGG. High-expressed *GPX7* can predict the sensitivity of TMZ in LGG patients.

**Keywords:** *GPX7*, pan-cancer, gene expression, prognosis, biomarker

## Introduction

Globally, cancer has become a major public health concern due to the increasing morbidity and mortality. According to statistics from the latest edition of the Global Cancer Report released by the International Agency for Research on Cancer (IARC), there were approximately 19.3 million new cancer cases and 10 million deaths worldwide in 2020.<sup>1</sup> Cancer is associated with a heavy economic and social burden, and seriously threatens human health and safety. Malignant tumor is a complex multi-step disease with extremely complex biological characteristics. Due to the concealment of early clinical symptoms, early diagnosis is still challenging and the prognosis is poor. Gliomas is the most common and aggressive primary central nervous system tumors, which accounted for 80.8% of patients. The prognosis of glioma is unfavorable.<sup>2</sup> Glioma are classified into grades I–IV by the World Health Organization (WHO) based on histopathological characteristics. Grades II/III are categorized as low-grade glioma (LGG) and grade IV is categorized glioblastoma (GBM).<sup>3</sup> Due to the highly invasive nature and incomplete surgical resection, tumor recurrence and progression to GBM are common in

LGG, which present a therapeutic challenge for doctors.<sup>4</sup> Therefore, identifying effective biomarkers of LGG is essential to guide comprehensive treatment.

The glutathione peroxidase (*GPXs*) family is an important member of the selenoprotein family. It is one of the important antioxidant enzymes, and an important reactive oxygen species (ROS) free radical scavenger in an organism. Studies have proved that *GPXs* usually use glutathione as a reducing substrate to catalyze the reduction of H<sub>2</sub>O<sub>2</sub> or organic hydroperoxide to water or the corresponding alcohol, respectively.<sup>5,6</sup> There are 8 types of *GPXs*, namely *GPX1–GPX8*, of which *GPX1–GPX4* and *GPX6* are *GPXs* containing selenocysteine, while *GPX5*, *GPX7* and *GPX8* are non-selenocysteine *GPXs*.<sup>5–8</sup> Mammalian glutathione peroxidase-7 (*GPX7*) is a non-selenocysteine containing phospholipid hydroperoxide glutathione peroxidase.<sup>7</sup> It plays an important role in maintaining the redox state.<sup>9,10</sup> When cells are exposed to oxidative stress, the unique pressure sensor function of *GPX7* can effectively detect redox levels and transmit ROS signals to redox sensitive cells and thiol-containing proteins, further promoting protein folding and releasing non-targeted short interfering RNAs (siRNAs) related stress.<sup>11</sup> The dysregulation of *GPX7* may lead to some diseases and even cancer. Previous studies have shown that the differential expression of *GPX7* is closely related to the occurrence and progression of multiple tumors. Experiments showed that *GPX7* protects esophageal epithelia from bile acids-induced oxidative DNA damage, double strand breaks and apoptosis in oesophagus cancer.<sup>12</sup> *GPX7* was overexpressed in hepatocellular carcinoma tissues.<sup>13</sup> *GPX7* had tumor suppression function in gastric cancer and was silenced by promoter DNA methylation.<sup>14</sup> The biological function of *GPX7* is quite important for basic biology studies. Although *GPX7* gene expression and its transcription characteristics have been explored in certain specific tumors, expression pattern of *GPX7* as well as its prognostic value have not been studied through the pan-cancer perspective.

Pan-cancer analysis does not refer to a specific tumor, instead, data from different tumor types and multiple sets of platforms are integrated, analyzed, and interpreted to identify and analyze different genetic changes in malignancies.<sup>15</sup> Through pan-cancer analysis, similarities and differences between genomes and cell changes for different malignant tumor types can be screened. In this study, taking advantages of the Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) databases, we comprehensively explored the expression pattern of *GPX7*, its value of prognostic, and its relationship with immune infiltration, tumor mutational burden (TMB) and microsatellite instability (MSI) through pan-cancer analysis. The prognostic potential of *GPX7* in LGG was fully explored and a nomogram was established to predict the survival outcome of LGG patients. Especially, the biological significance of *GPX7* for the possibility to determine sensitivity of chemoradiotherapy in LGG also explore in our present study.

## Materials and Methods

### Raw Data Collection

RNA-seq data from the Human Protein Atlas (HPA) (<https://www.proteinatlas.org/>) was used to explore the expression pattern of *GPX7* in human normal tissues and cell lines. The mRNA expression data of *GPX7* in tumor tissues were downloaded from TCGA database (<http://cancergenome.nih.gov/>). TCGA performed molecular profiling of more than 20,000 primary cancers, covering 33 tumor types and matching normal samples from 33 cancer types. In order to explore the expression differences of *GPX7* in different cancer types and corresponding normal tissues, we obtained normal tissue samples matching 33 TCGA cancer types from the GTEx (<https://www.gtexportal.org/home/>) database, and then combined GTEx data with TCGA data. The transcriptome and clinical data of glioma patients were obtained from the Chinese Glioma Genome Atlas (CGGA) database (<http://www.cgga.org.cn/>) to verify the expression level of *GPX7* in LGG and the prognostic outcome of LGG patients. The information about temozolomide (TMZ) sensitivity in LGG was collected from the Genomics of Drug Sensitivity in Cancer (GDSC, <https://www.cancerrxgene.org/>) database.

### GPX7 Expression Profiles in Human Normal Tissues and Cell Lines

The HPA database was a comprehensive resource website that provided the expression and distribution of more than 17,000 individual proteins in all kinds of cells, tissues and organs.<sup>16</sup> In the present study, *GPX7* mRNA expression and distribution in human normal tissues (n=55) and all cell lines (n=69) used the HPA database to evaluate.

## GPX7 Expression Pattern in Human Tumor Tissues

The RNA-seq expression data of 33 tumors with matched normal tissues were obtained from the TCGA database.<sup>17</sup> The mRNA expression data of normal tissues were downloaded from the GTEx database.<sup>18</sup> The expression profile of *GPX7* was analyzed through the integrated data of GTEx and TCGA. The difference between the tumor tissues and the normal tissues was analyzed by rank sum test, and the  $P < 0.05$  was considered statistically significant. The R software V 4.0.3 was used for statistical analysis. Data were visualized as violin plots.

UALCAN database (<http://ualcan.path.uab.edu/analysis-prot.html>) was an interactive web-portal for analyzing cancer OMICS data of TCGA.<sup>19</sup> In the present study, the UALCAN database was used to explore gene expression at the protein level. The expression profile of *GPX7* protein in 10 different tumors was retrieved used the CPTAC module, including: breast invasive carcinoma (BRCA), ovarian serous cystadenocarcinoma (OV), colon adenocarcinoma (COAD), kidney renal clear cell carcinoma (KIRC), uterine corpus endometrial carcinoma (UCEC), lung adenocarcinoma (LUAD), head and neck squamous cell carcinoma (HNSC), pancreatic adenocarcinoma (PAAD), GBM and liver hepatocellular carcinoma (LIHC). The expression profile of *GPX7* protein was presented by box plots. Z-values represented standard deviations (SD) from the median (M) across samples for a particular cancer type.

## Association Between *GPX7* Protein Expression Level and Clinicopathological Parameters

Analysis data of *GPX7*-relevant proteomic characteristics, such as tumor stage, age, race and gender were downloaded from the “CPTAC Analysis” module of UALCAN. Z-values represent standard deviations (SD) from the median (M) across samples of a certain cancer and they were used to evaluate association between *GPX7* protein expression level and clinicopathological parameters.

## Survival and Prognosis Analysis

The “Survival map” module of the Gene Expression Profiling Interactive Analysis (GEPIA2)<sup>20</sup> (<http://gepia.cancer-pku.cn/index.html>) was used to obtain overall survival (OS) and disease-free survival (DFS) significant survival curves of *GPX7* in 33 TCGA tumors. The cutoff-high (50%) and cutoff-low (50%) values were defined as thresholds to group the whole cohort into high and low expression groups respectively. Kaplan-Meier survival curves were established by the “survival analysis” module of GEPIA2. Log rank test was used to perform hypothesis testing, and determine differences between Log rank test curves. Univariate Cox regression was used to calculate hazard ratios (HR) and 95% confidence interval (95% CI). The significance level was set at 0.05. Survival analysis (OS, DFS, progression-free survival (PFS) and disease specific survival (DSS)) used the “ggforest” in the R-package “survminer” to form forest plots to further evaluate the prognostic potential of *GPX7* expression in patients with different tumors.

The CGGA was an open-access platform that collected a multi-dimensional functional genomic dataset of nearly 2000 glioma samples from Chinese cohorts.<sup>21</sup> In this study, the CGGA database was used to further evaluate and verify the relationship between *GPX7* expression and prognostic potential in glioma.

## Correlation Between *GPX7* and Infiltration of Immune Cells

Exploring the correlation between *GPX7* and immune infiltration is of great significance for further basic biological research. RNA-seq data from the TCGA database were analyzed by Immuneconv to explore the correlation between *GPX7* and immune infiltration.<sup>22</sup> Immuneconv R package can be obtained from github (<https://github.com/icbi-lab/immuneconv/issues>). It is often used to evaluate the immune cell components in tumor tissue and it integrates six of the latest algorithms. The EPIC algorithm was often used to explore the level of immune infiltration in most solid tumors. It can explain non-characteristic cells and the mRNA content in each cell type.<sup>23</sup> In the present study, EPIC algorithm was used to evaluate the potential correlation between immune cell (CD8+T cell, CD4+T cell, NK cell, Macrophage, Endothelial cell, and B cell) infiltration levels and expression levels of *GPX7*. R software V4.0.3 was used for statistical analysis, and  $P < 0.05$  was considered statistically significant.

TIMER 2.0 (<http://timer.cistrome.org/>) was an interactive web application that was used to comprehensively and flexibly analyze the richness of tumor infiltrating immune cells.<sup>24</sup> In this study, the “Immune-gene” module of TIMER 2.0 was used to determine the association between *GPX7* expression and cancer-associated fibroblasts (CAFs) infiltration level of TCGA tumors based on four algorithms including EPIC, MCPOUNTER, XCELL and TIDE. When the results of four algorithms were all statistically significant, a scatter plot with the highest correlation coefficient was given. R software V 4.0.3 was used for statistical analysis.  $P < 0.05$  was considered statistically significant.

## Gene Mutation Analysis

TMB can predict the immune checkpoint inhibitor response.<sup>25</sup> MSI, a genetic hypermutation state caused by the inactivation of mismatch repair genes, is a known immunotherapy biomarker.<sup>26</sup> In this study, the somatic mutation profiles of all tumor patients were extracted from the Genomic Data Commons (GDC) (<https://portal.gdc.cancer.gov/>)<sup>27</sup> data portal website of TCGA database to calculate the TMB score and MSI score. The association between the expression of *GPX7* and TMB/ MSI was further explored. Statistical analysis was performed using the R software V 4.0.3, and the difference of the two groups were determined by rank sum test.  $P < 0.05$  was considered statistically significant.

## Prognostic Nomogram for LGG

We used univariate and multivariate Cox regression analysis to screen independent prognostic factors to further explore the association between *GPX7* expression and prognosis in LGG. Based on the results of multivariate Cox regression analysis, the nomogram was established using the “rms” R package to predict the OS of LGG patients. Perform ROC analysis on the risk score of the multivariate Cox model to obtain the Concordance index (C-index), which was used to quantify the efficacy of the nomogram for prognostic evaluation. The closer the C-index was to 1, the better the nomogram predictive ability. The calibration plots were a comparison between the risk predicted by the nomogram and the actual risk of patient. The closer the predicted curve was to the standard curve, the better the predictability of the model.

## The Effect of the Interaction of *GPX7* with Chemoradiotherapy on Prognosis in LGG

Based on *GPX7* mRNA data from TCGA LGG patients, we explored the effect of the interaction of *GPX7* with chemoradiotherapy on the prognosis of the patients. The difference between the different groups was analyzed by rank sum test. The correlation between *GPX7* expression and TMZ sensitivity in LGG was also analyzed by TCGA and GDSC database.<sup>28</sup> The half-maximal inhibitory concentration (IC<sub>50</sub>) of TMZ was calculated by ridge regression. All the above analysis process were performed by R 4.0.3.  $P < 0.05$  was considered statistically significant.

## Results

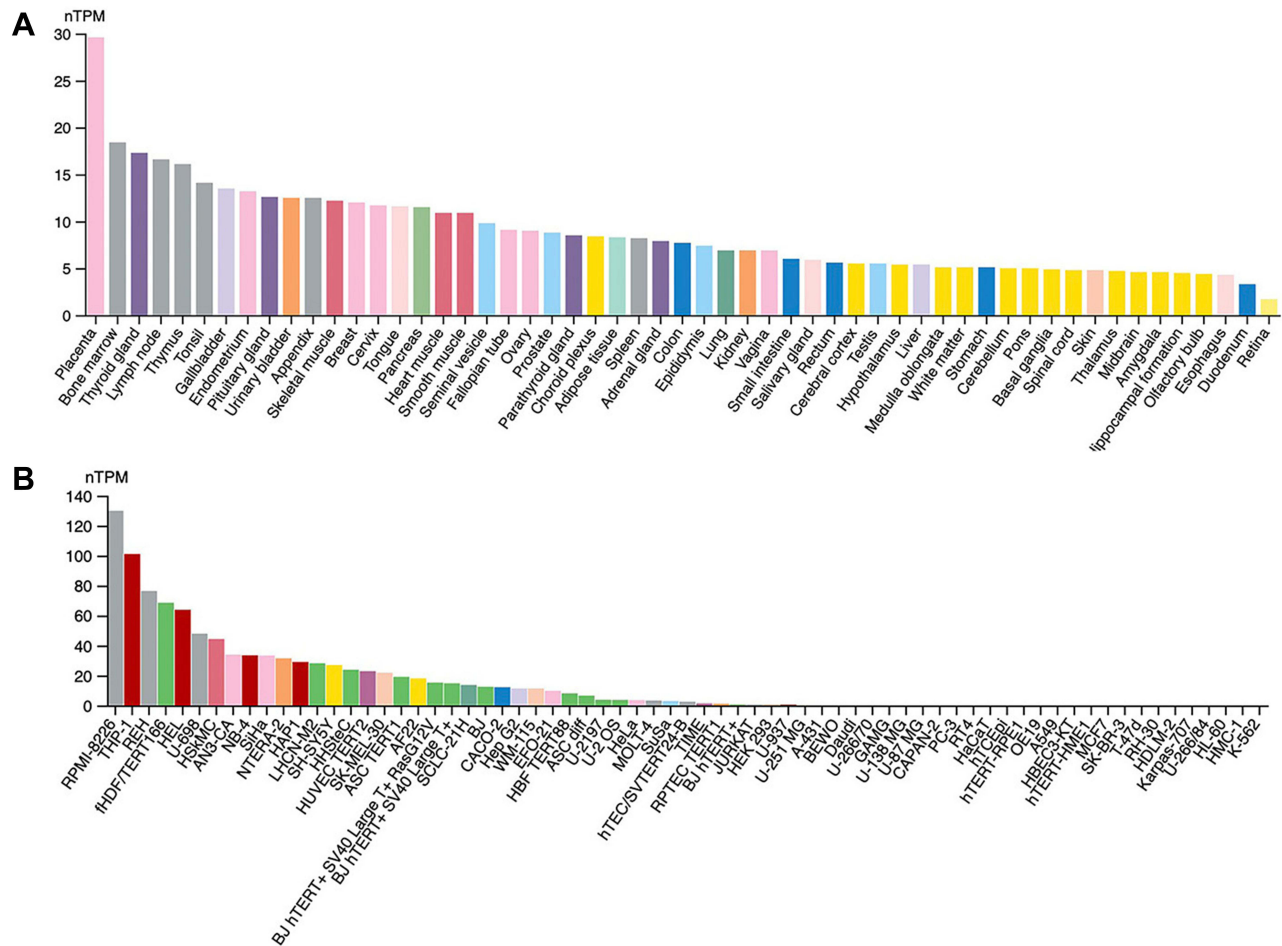
### *GPX7* mRNA Expression and Distribution in Human Normal Tissues and Cell Lines

The tissue atlas from the HPA database was used to analyze the mRNA expression of *GPX7* in human tissues and cell lines (Figure 1). Analysis showed that *GPX7* mRNA was widely distributed in normal human tissues (Figure 1A) and cell lines (Figure 1B). These findings show that there is no specificity in mRNA expression of *GPX7* in the human body, including tissues and cell lines.

### The Expression Levels of *GPX7* in Human Tumor Tissues

The expression levels of *GPX7* mRNA in 33 tumor tissues and matched normal tissues were compared using TCGA and GTEx datasets (Figure 2). The results showed that with the exception of the 3 types of tumors, the expression difference between tumor tissues and normal tissues was statistically significant ( $P < 0.05$ ). Analysis showed that compared to normal tissues, mRNA expression of *GPX7* were over-expressed in 22 human tumor tissues, including BRCA, esophageal carcinoma (ESCA), GBM, LGG, LIHC. In contrast, *GPX7* mRNA expression were under-expressed in kidney chromophobe (KICH) and prostate adenocarcinoma (PRAD).

The expression of *GPX7* protein levels were analyzed using the CPTAC database (Figure 3). The results showed that *GPX7* protein is highly expressed in 9 types of tumors, including BRCA, COAD, KIRC, UCEC, LUAD and HNSC ( $P < 0.05$ ).



**Figure 1** Expression levels and distribution of *GPX7* mRNA in human normal tissues from HPA database. **(A)** mRNA expression level of *GPX7* across 55 different normal tissues. **(B)** mRNA expression level of *GPX7* across 69 different cell lines.

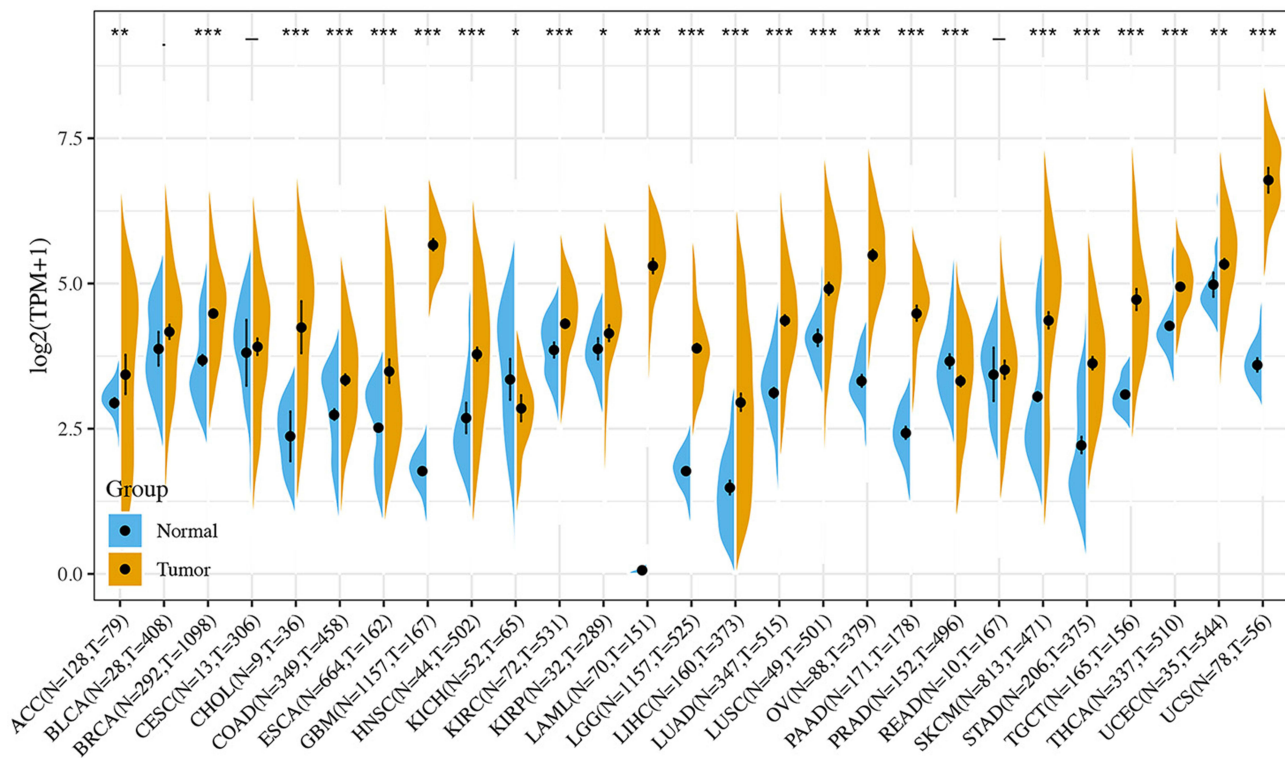
## Association Between *GPX7* Protein Expression and Pathological Parameters

The data related to the expression of *GPX7* protein and age, gender, race and cancer stage was obtained from the UALCAN dataset (Figure 4). Results showed that expression level of *GPX7* protein exhibited a gradually increasing trend in COAD, OV, KIRC and UCEC. That is, the highest expression was found in stage IV (Figure 4A). Expression levels of the *GPX7* protein in OV, COAD, KIRC, UCEC and LUAD were generally elevated in Caucasian patients than in other races (Figure 4B). In terms of age, elevated expression levels of the *GPX7* protein were increased in people aged 20 to 40 years in BRCA, OV, COAD and KIRC (Figure 4C). In terms of gender, expression levels of the *GPX7* protein were increased in males than in females in COAD and LUAD (Figure 4D).

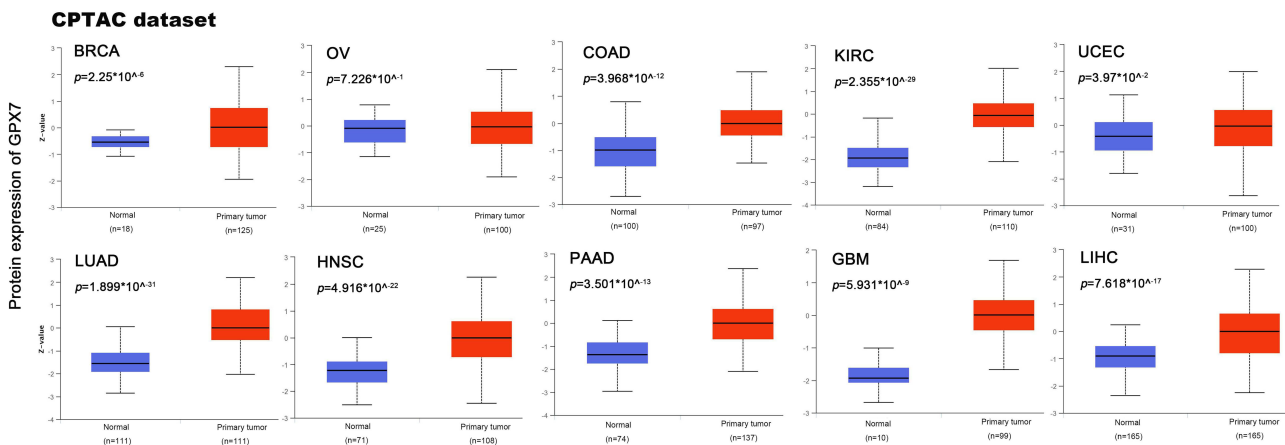
## Prognostic Value of *GPX7* in Human Tumors

The association between the expression of *GPX7* and prognosis of human tumors was analyzed using TCGA database (Figure 5). Kaplan-Meier survival curves showed that *GPX7* overexpression was correlated with poor OS in LGG ( $P = 4.4e-08$ ), LIHC ( $P = 0.022$ ), mesothelioma (MESO) ( $P = 4e-04$ ), sarcoma (SARC) ( $P = 0.015$ ) and stomach adenocarcinoma (STAD) ( $P = 0.0096$ ) (Figure 5A). DFS analysis showed that *GPX7* was correlated with poor prognosis with high expression levels in LGG ( $P = 3.6e-05$ ), SARC ( $P = 0.015$ ) and STAD ( $P = 0.0096$ ) (Figure 5B). These results indicate that *GPX7* overexpression is a risk factor for poor prognosis in LGG patients regarding OS and DFS.

We used Cox regression model to further verify prognostic value of *GPX7* on the survival outcomes (OS, PFS, DFS, DSS) of patients with different tumors (Figure 6). Elevated expression levels of *GPX7* were significantly associated with



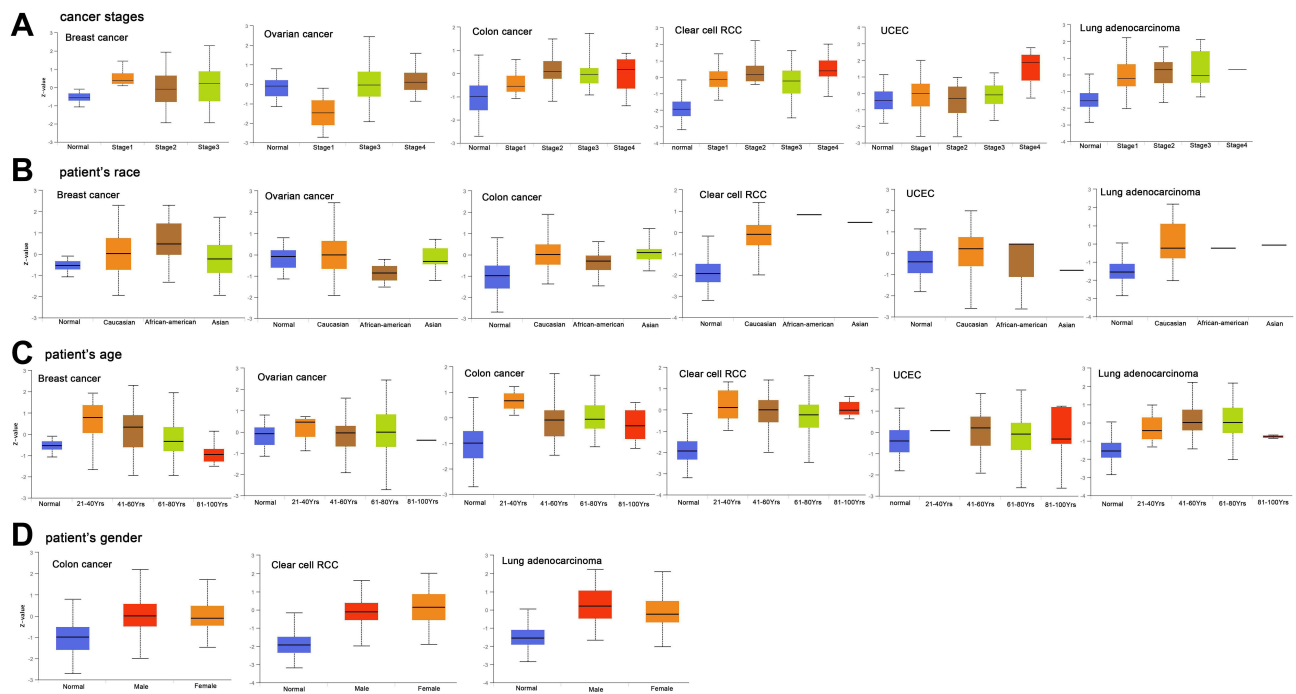
**Figure 2** mRNA expression level of GPX7 in human tumor tissues and normal tissues from TCGA database and GTEx database. \*p<0.05; \*\*p<0.01; \*\*\*p<0.001; "-" insignificant.



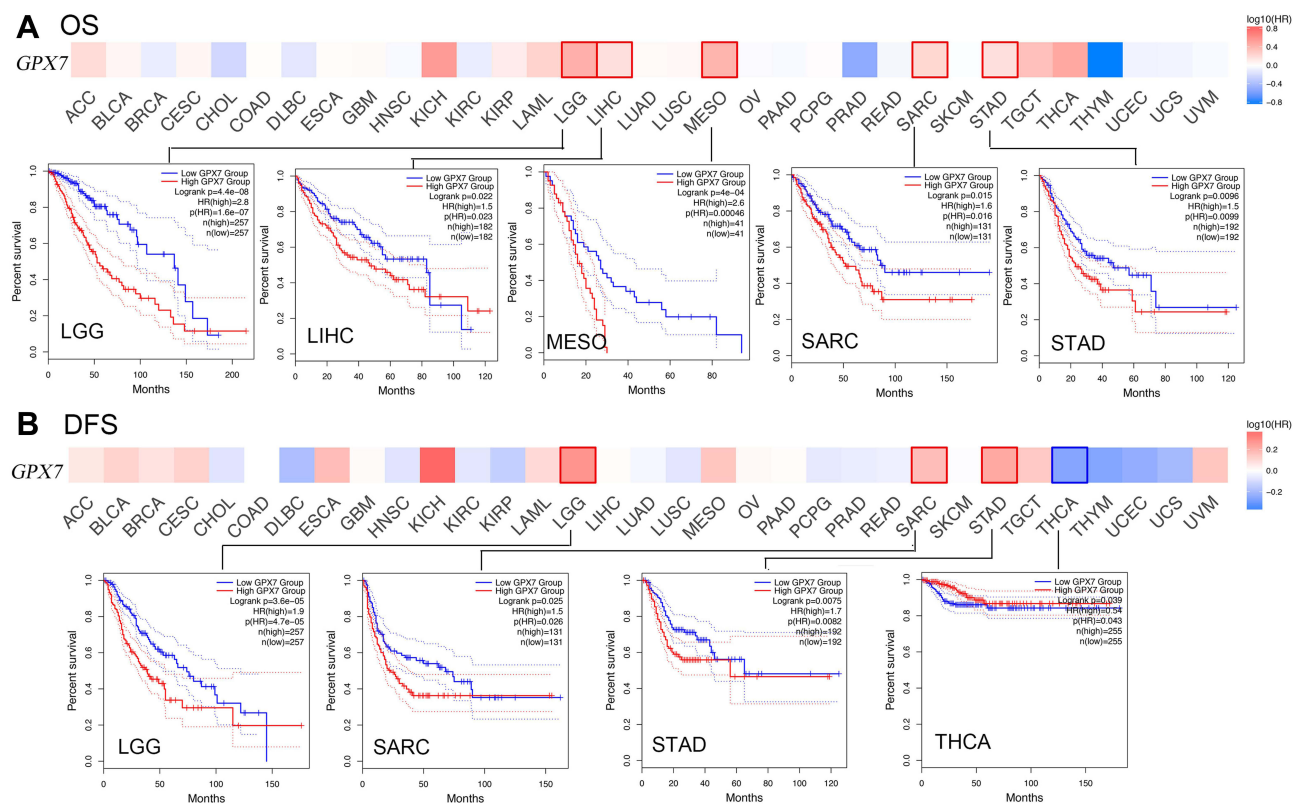
**Figure 3** Expression level of GPX7 protein in the normal tissues and primary tumors tissues from CPTAC database.

poor prognosis in bladder urothelial carcinoma (BLCA), KICH, LGG, SARC and STAD regarding OS, DFS and PFS. In adrenocortical carcinoma (ACC) and MESO, elevated expression levels of *GPX7* were associated with poor OS and PFS. In contrast, elevated expression levels of *GPX7* in thymoma (THYM) were correlated with better OS and PFS outcomes (Figure 6A–C). In kidney renal papillary cell carcinoma (KIRP) and PAAD, elevated expression levels of *GPX7* were associated with poor DSS (Figure 6D). The results of integrating Kaplan-Meier survival curves and Cox regression forest plot suggested that *GPX7* was significantly associated with poor prognosis of OS, DFS and PFS in LGG, SARC and STAD. In general, elevated *GPX7* expression levels were associated with poor clinical outcomes in most tumors.

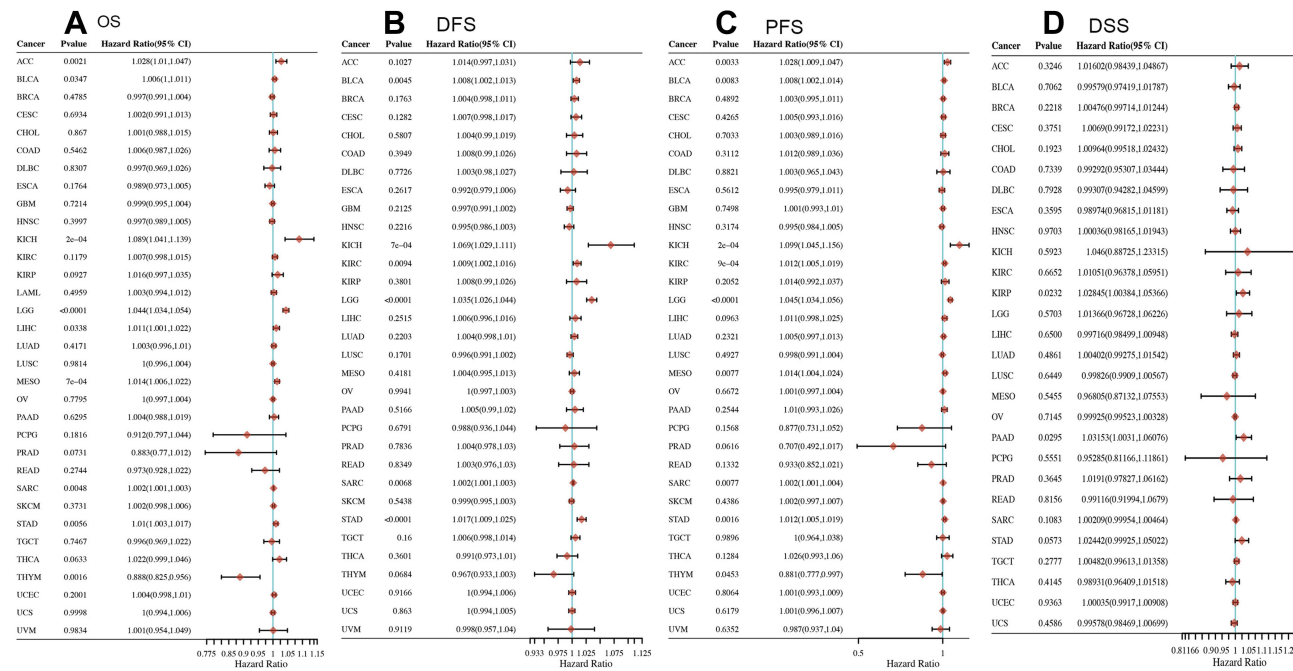
The above survival analysis results indicated that the high expression of *GPX7* was closely related to the poor prognosis of LGG patients. Therefore, we downloaded the glioma dataset from the CGGA database to further verify the



**Figure 4** The relationship between GPX7 protein expression and clinicopathological parameters. **(A)** The relationship between GPX7 protein expression and cancer stage. **(B)** The relationship between GPX7 protein expression and patients' race. **(C)** The relationship between GPX7 protein expression and patients' age. **(D)** The relationship between GPX7 protein expression and patients' gender.  $P < 0.05$  was considered statistically significant.



**Figure 5** Kaplan-Meier survival curves of high and low expression of GPX7 in different types of tumors. **(A)** OS in LGG, LIHC, MESO, SARC, STAD. **(B)** DFS in LGG, SARC, STAD, THCA.



**Figure 6** Forest plot for association between *GPX7* and OS (A), DFS (B), PFS (C), DSS (D) in patients with different tumor types from TCGA database.  $P < 0.05$  was considered statistically significant.

prognostic value of *GPX7* in LGG. The cohort consisted of 182 LGG cases and 139 GBM cases (Figure 7). Analysis showed that the expression levels of *GPX7* gradually increased as the disease progresses ( $P = 2.4e-34$ , Figure 7A). Survival analysis showed that overexpression of *GPX7* was correlated with poor prognosis in LGG ( $P < 0.0001$ , Figure 7B), which is consistent with the results of TCGA analysis.

### Relationship Between *GPX7* Expression and Immune Infiltration

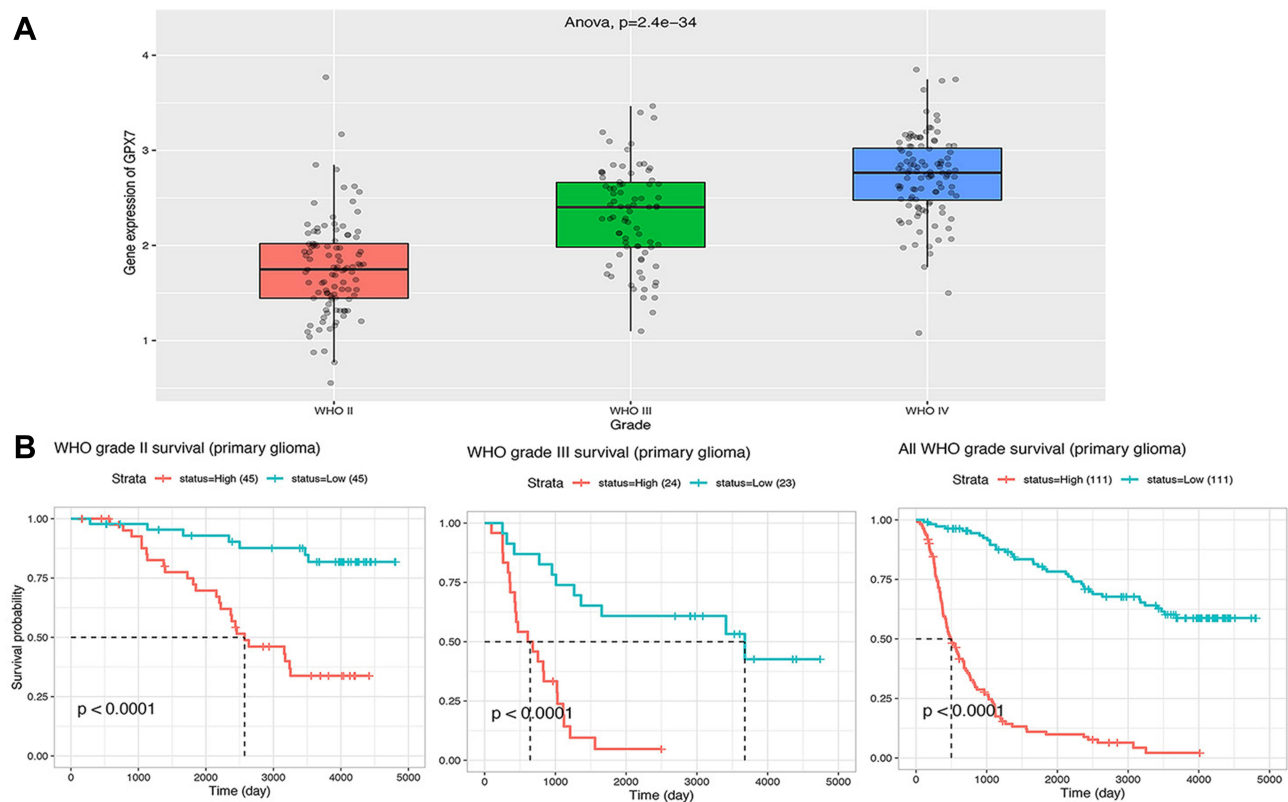
The tumor microenvironment is crucial to the occurrence and development of tumors as well as to basic biological research. In this study, the EPIC algorithm was used to explore the correlation between *GPX7* and immune infiltration (Figure 8A). Results showed that there was an overall positive correlation between *GPX7* expression and endothelial cell, macrophage in most tumors. Expression of *GPX7* was positively correlated with macrophage, endothelial cell and B cell infiltrations in BRCA, COAD, HNSC, PAAD and STAD. In LGG, *GPX7* expression was negatively correlated with CD4+T cell, CD8+T cell and B cell infiltrations and it was positively correlated with macrophage infiltrations.

The TIMER 2.0 interactive web tool was used to explore the relationship between *GPX7* expression and CAFs infiltration in different tumors based on four different algorithms (Figure 8B). Analysis showed that *GPX7* expression and CAFs abundances were positively correlated in 20 tumors, including BLCA, BRCA, BRCA-LumA, BRCA-LumB, Cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC).

### Relationships Between *GPX7* and TMB/MSI

The relationship between *GPX7* and TMB is shown in Figure 9A. The expression of *GPX7* was positively correlated with TMB in 8 tumors, including LGG ( $R = 0.366$ ,  $P = 1.15e-17$ ) and OV ( $R = 0.148$ ,  $P = 0.019$ ). In contrast, the expression of *GPX7* was negatively correlated with TMB in 24 tumors, including PRAD ( $R = -0.336$ ,  $P = 4.31e-14$ ), STAD ( $R = -0.284$ ,  $P = 3.26e-08$ ), uveal melanoma (UVM) ( $R = -0.249$ ,  $P = 0.026$ ), ESCA ( $R = -0.24$ ,  $P = 0.002$ ), THYM ( $R = -0.223$ ,  $P = 0.016$ ), skin cutaneous melanoma (SKCM) ( $R = -0.196$ ,  $P = 2.26e-05$ ), LIHC ( $R = -0.171$ ,  $P = 0.002$ ), PAAD ( $R = -0.16$ ,  $P = 0.043$ ), HNSC ( $R = -0.14$ ,  $P = 0.001$ ), COAD ( $R = -0.11$ ,  $P = 0.039$ ) and thyroid carcinoma (THCA) ( $R = -0.109$ ,  $P = 0.017$ ). The relationship between *GPX7* and MSI is shown in Figure 9B. Analysis showed that there was a positive correlation between *GPX7* and MSI in 14 tumors, including testicular germ cell tumors (TGCT) ( $R = 0.18$ ,  $P = 0.038$ ). On the other hand, the expression level of *GPX7* was





**Figure 7** The expression pattern of *GPX7* and the prognostic potential in glioma patients from CGGA database. **(A)** Expression level of *GPX7* in LGG and GBM. **(B)** Kaplan-Meier survival curves of high and low expression of *GPX7* in primary LGG and all WHO grade primary glioma.

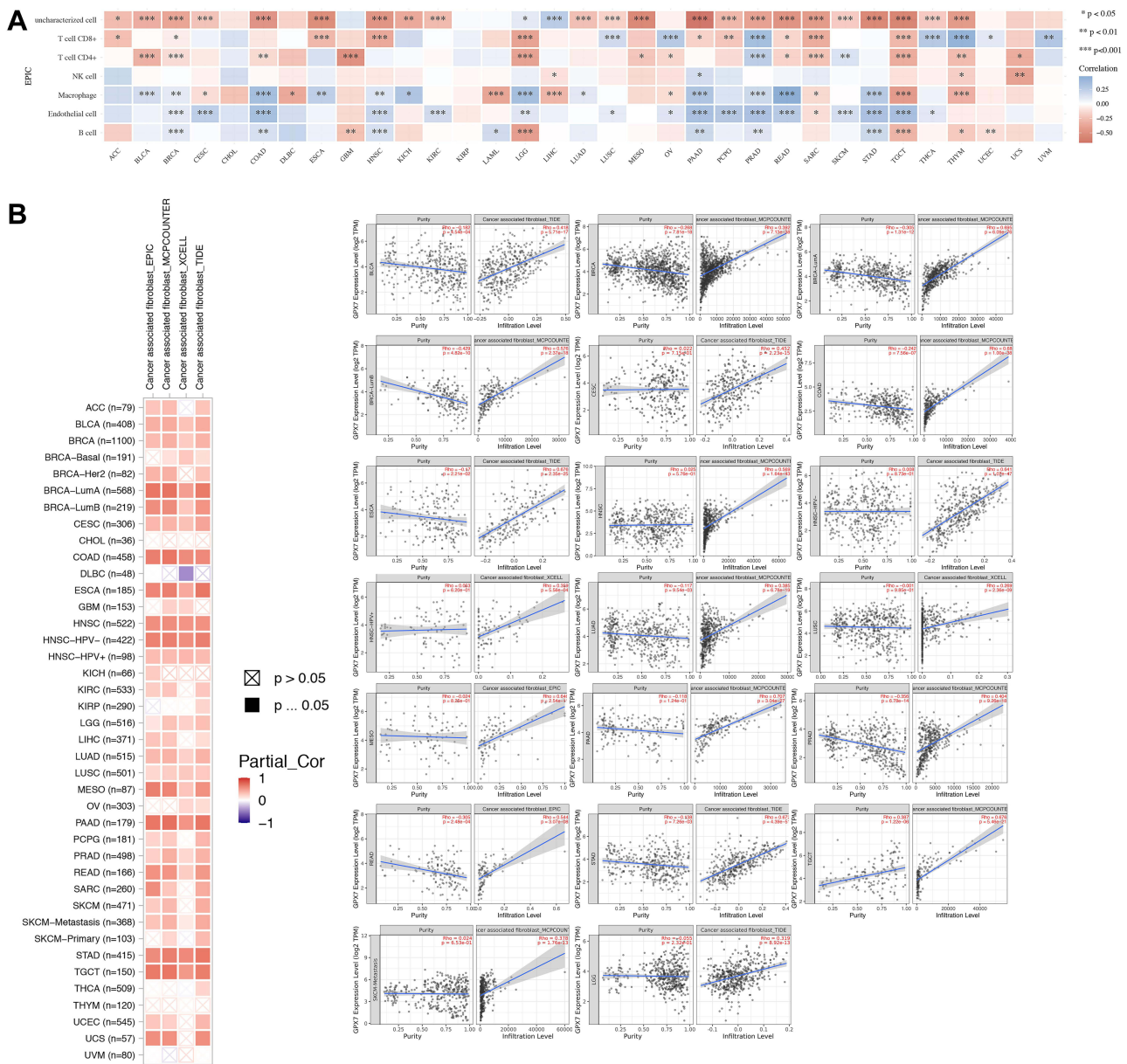
negatively correlated between *GPX7* and MSI in 19 tumors, including lymphoid neoplasm diffuse large B-cell lymphoma (DLBC) ( $R = -0.296$ ,  $P = 0.041$ ), STAD ( $R = -0.221$ ,  $P = 1.58e-05$ ) and LUAD ( $R = -0.191$ ,  $P = 1.35e-05$ ). It is worth noting that the correlation coefficients between *GPX7* and TMB was the highest in the LGG cohort.

## Development and Validation of Prognostic Nomogram for LGG

The above results strongly support that there was a significant correlation between the expression of *GPX7* and the prognosis of LGG. Therefore, a nomogram was developed and verified the value of *GPX7* mRNA expression level on the prognosis potential of LGG patients. The TCGA cohort was used to perform univariate and multivariate Cox regression analysis on LGG patients to determine the independent prognostic factors of LGG patients. *GPX7* and age were significantly correlated with OS in LGG patients through univariate Cox regression analysis ( $P < 0.0001$ , Figure 10A). Multivariate Cox regression analysis showed that age and *GPX7* were identified as independent prognostic factors for LGG ( $P < 0.0001$ , Figure 10B). Based on the results of multivariate Cox regression analysis, the nomogram was established predict the 1-year, 2-year, 3-year, and 5-year OS of LGG patients (Figure 10C). The C-index of the nomogram model was 0.845 (95% CI, 0.825 to 0.865;  $P < 0.001$ ), indicated that this model has a high predictability. The Calibration plots curve showed that the predicted survival outcome of LGG nomogram matches the observed actual survival outcome well (Figure 10D). These results indicated that this nomogram model was a good predictor of the OS of LGG patients, which strongly supports that *GPX7* was a prognostic indicator for LGG patients.

## The Effect of the Interaction of *GPX7* with Chemoradiotherapy on Prognosis in LGG

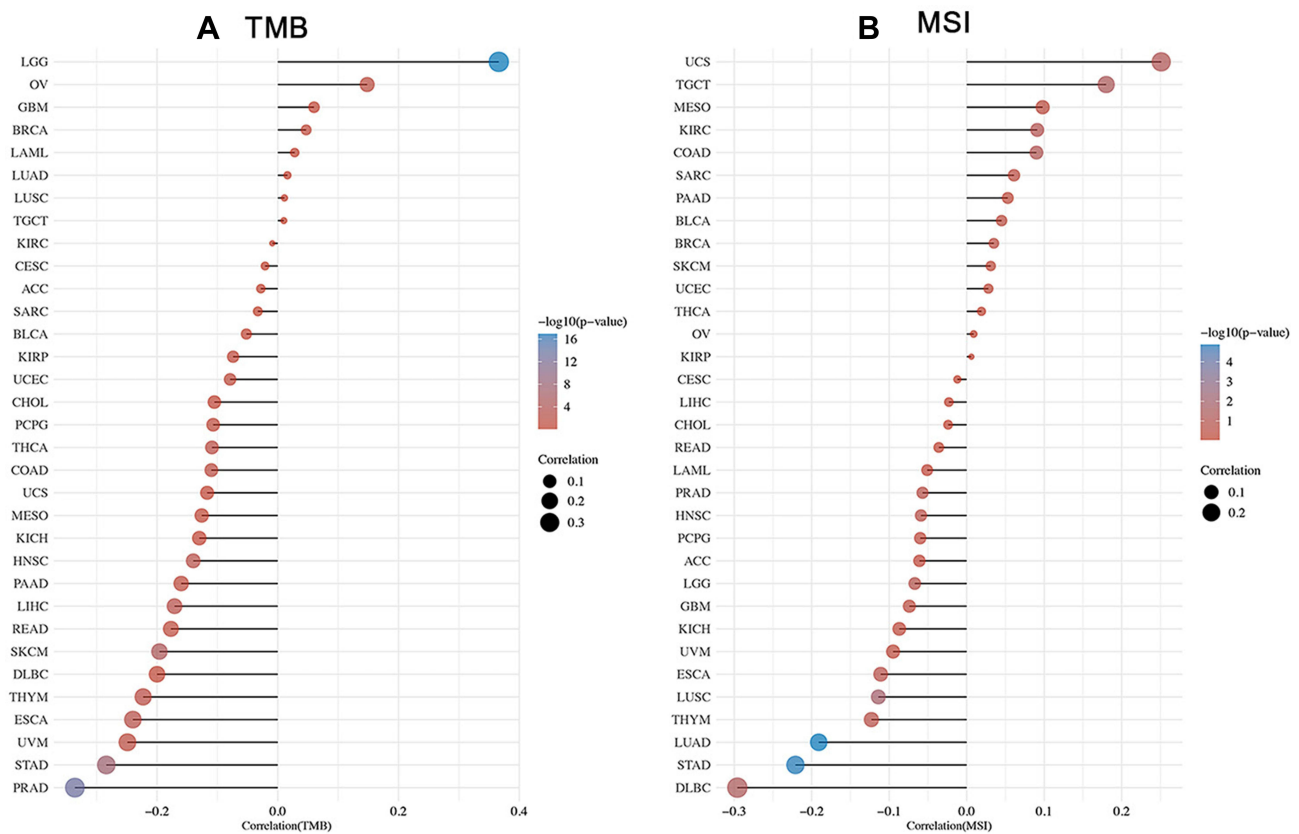
The effect of the interaction of *GPX7* with chemoradiotherapy on prognosis in LGG was explored by TCGA dataset ( $n=510$ ). In radiotherapy (RT) group ( $n=142$ ), high-expression of *GPX7* with a  $\log_2(x+0.001)$  value bigger than 4.31 was correlated with poor overall survival ( $P < 0.05$ , Figure 11A). In chemotherapy group ( $n=223$ ), high-expression of *GPX7*



**Figure 8** Correlation between *GPX7* expression and immune cells infiltration in 33 TCGA tumors. **(A)** Correlation between *GPX7* expression and infiltration level of six important immune cells as determined by the EPIC algorithm. \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ . **(B)** Correlation between *GPX7* expression and immune infiltration of CAFs.

with a  $\log_2(x+0.001)$  value higher than 4.37 was also associated with poor clinical outcomes ( $P < 0.05$ , Figure 11B). Subsequently, the patients with *GPX7* high-expression ( $n=126$ ) were divided into RT group ( $n=87$ ) and non-RT group ( $n=39$ ). There was no statistical difference in OS between the two groups, but a trend of shorter OS was found in RT group ( $P > 0.05$ , Figure 11C).

In order to explore potential significance of elevated *GPX7* for the sensitivity of chemoradiotherapy in LGG, the correlation between *GPX7* expression and TMZ sensitivity in LGG patients was analyzed. The results showed that *GPX7* expression was negatively correlated with TMZ IC50 ( $\hat{\rho}_{\text{spearman}} = -0.59$ ,  $P = 1.3e-48$ , Figure 11D), which suggested that high-expressed *GPX7* can predict the sensitivity of TMZ in LGG patients.

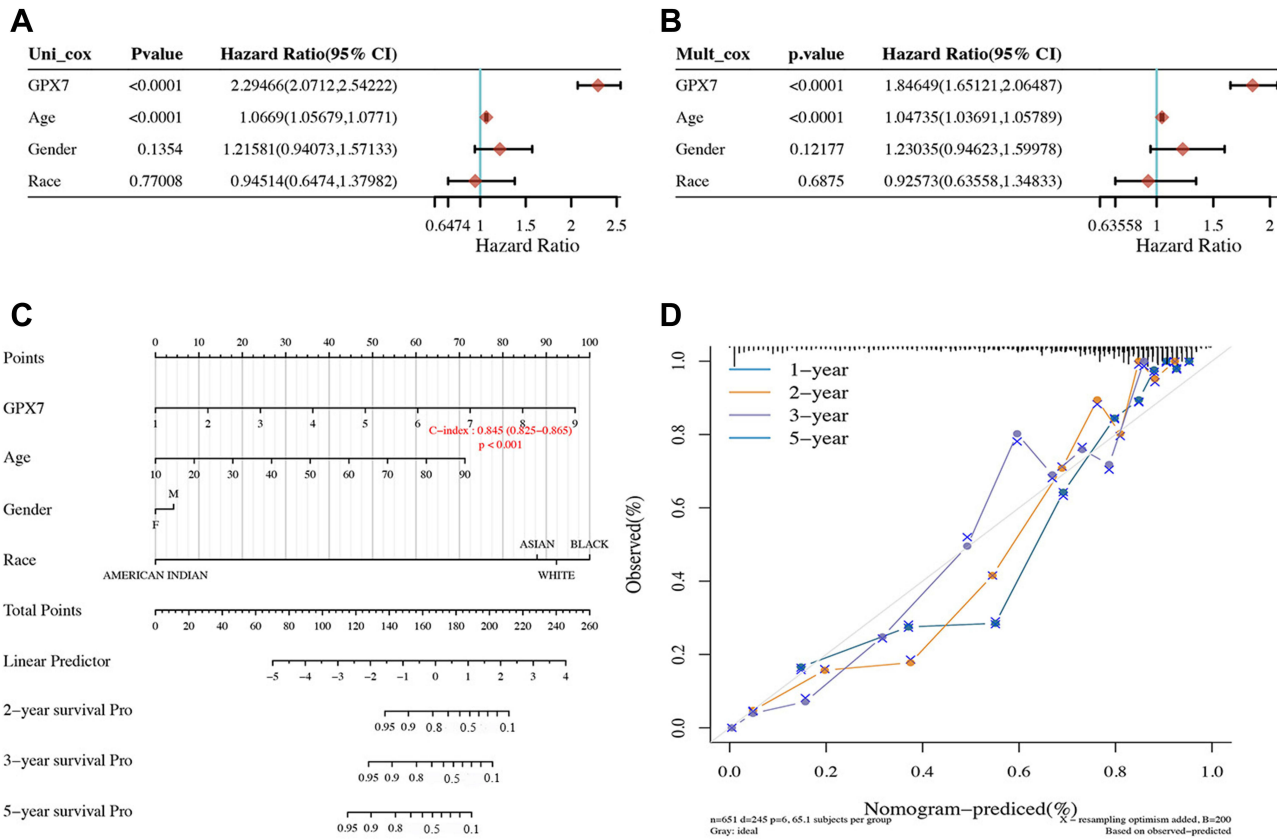


**Figure 9** The correlations between *GPX7* expression and TMB (A)/MSI (B) across TCGA 33 tumors. The significance of the P value is represented by different colors, and the color from blue to red represents the significance from small to large. The Spearman correlation coefficient is shown by the size of the dots. The larger the dot, the larger the correlation coefficient.

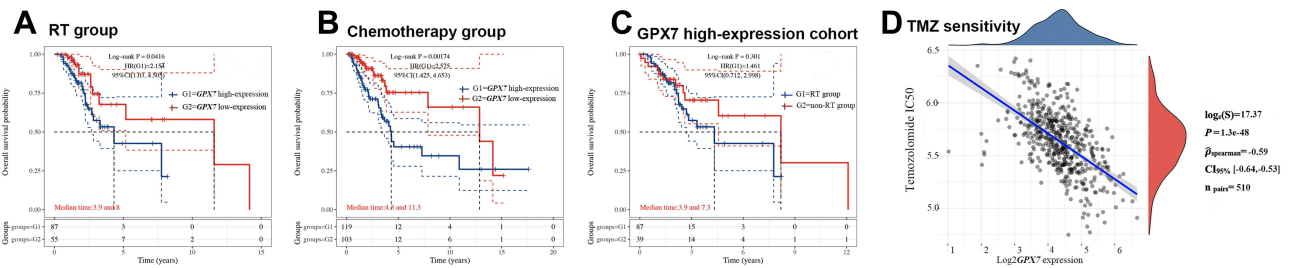
## Discussion

*GPXs* family is an important member of the selenoprotein family. *GPXs* is one of the most important enzyme families that involve in ROS removing process. *GPXs* plays an important role in the antioxidant system by scavenging  $H_2O_2$ , organic peroxides and lipid peroxides.<sup>29</sup> *GPX7*, a newly discovered non-selenium-containing member of the *GPXs* family, is free near the endoplasmic reticulum and is one of the proteins with lower glutathione peroxidase activity.<sup>8,30</sup> It has a high amino acid sequence homology with other family members.<sup>5,7</sup> The sequence of *GPX7* encodes cysteine in its conserved catalytic motifs.<sup>11</sup> *GPX7* maintains the redox state and participates in protein folding in the body.<sup>6,7</sup> Exploring the biological function of *GPX7* is of great significance for further basic biological research. Emerging evidence indicates that differences in *GPX7* expression are related to the occurrence and development of certain tumors, such as breast cancer,<sup>7</sup> gastric cancer<sup>14</sup> and hepatocellular adenocarcinoma.<sup>13</sup> However, the expression profile and prognostic value of *GPX7* has not been reported from a pan-cancer perspective. Therefore, this study integrates data from multiple online databases to comprehensively explore the expression pattern and prognostic value of *GPX7*.

The expression of *GPX7* in human normal tissues does not show specificity, which provides a basis for further basic biological research. Multiple studies have explored the relationship between *GPX7* and specific tumors.<sup>14,31,32</sup> Our study revealed that the expression of *GPX7* was elevated in multiple tumor tissues, including LGG, GBM, BRCA, ESCA, LIHC. Yao et al reported that the expression of *GPX7* was higher in glioma tissue compared with normal brain tissue.<sup>32</sup> Previous studies have shown that *GPX7* has potential tumor suppressor effects in gastric cancer and esophageal adenocarcinoma.<sup>12,14,33</sup> Down-regulation and dysfunction of *GPX7* expression in esophageal cells increase ROS level and oxidative DNA damage.<sup>33</sup> In hepatocellular carcinoma *GPX7* expression was also elevated. Moreover, *GPX7*



**Figure 10** Construction and validation of the prognostic nomogram model for LGG based on TCGA database. (A) Univariate Cox proportional hazards regression analysis of clinical parameters with OS of LGG patients. (B) Multivariate Cox proportional hazards regression analysis of clinical parameters with OS of LGG patients. (C) Prognostic nomogram to predict 2-year,3- year and 5-year OS rate of LGG patients. (D) Calibration curves of the prognostic nomogram for the overall survival of LGG patients.



**Figure 11** The interaction of *GPX7* with chemoradiotherapy on LGG prognosis and correlation between *GPX7* and TMZ sensitivity. (A) RT group: high-expression vs low-expression of *GPX7*, threshold:  $\log_2(x+0.001)$  value=4.31. (B) Chemotherapy group: high-expression vs low-expression of *GPX7*, threshold:  $\log_2(x+0.001)$  value=4.37. (C) High expression of *GPX7* cohort,  $\log_2(x+0.001)$  value  $\geq 4.375$ : RT group vs non-RT group. (D) Scatter plot between *GPX7* and TMZ IC50.

expression in stage III hepatocellular carcinoma tissues were significantly higher than that in stage I–II hepatocellular carcinoma tissues.<sup>13</sup> These findings were consistent with ours, which revealed that *GPX7* function is active in these tumors. In addition, we confirmed that *GPX7* expression was correlated with tumor stage. As the disease progressed, mRNA and protein expression level of *GPX7* exhibited an upward trend.

Elevated expression levels of *GPX7* were also associated with poor prognosis in certain tumors, such as LGG, SARC and STAD. It has also been reported the expression of *GPX7* in glioma tissues was higher than those in normal brain tissues. Elevated expression of *GPX7* led to poor prognosis of glioma patients.<sup>32</sup> These findings are consistent with ours. In GBM and LGG tissues, we found that expression of *GPX7* was significantly increased using TCGA and CGGA databases. Univariate and multivariate Cox regression analysis showed that *GPX7* were significantly correlated with OS

in LGG patients. In addition, in order to verify the above findings, we tried to use another independent analysis method to further verify. Nomogram is a powerful tool that has been widely used to predict an individual's prognosis.<sup>34,35</sup> Therefore, relevant prognostic factors were used to establish a nomogram to verify the correctness of the above results. Calibration plots revealed a good agreement between the nomogram prediction and actual observations in terms of the 1,2,3 and 5-year survival rates. These findings suggested that *GPX7* played a vital role in the progression of LGG. *GPX7* is identified as a novel prognostic indicator for LGG.

Exploring the relationship between *GPX7* and immune infiltration is of great significance for further basic biological research. Previous studies have found that *GPX*-related genes play a regulatory role in the immune process.<sup>36</sup> The *GPX7* expression level and redox homeostasis of *GPX7* are closely related to the body's autoimmunity.<sup>11</sup> ROS regulates the activity of immune cells. Once redox is unbalanced, it can easily lead to excessive activation of immune cells.<sup>37,38</sup> In this study, *GPX7* was positively correlated with macrophage, endothelial cell and B cell infiltrations in digestive tract tumors, including COAD, PAAD, rectum adenocarcinoma (READ) and STAD. Therefore, we speculate that the overexpression of *GPX7* is closely related to the over-oxidation of digestive system tumors. Studies have shown that ROS levels are higher in digestive system tumors, such as colorectal cancer,<sup>39</sup> pancreatic cancer<sup>40</sup> and gastric cancer.<sup>41</sup> A certain threshold of *GPX7* in tumor tissues has a strong anti-inflammatory antioxidant role, which may be in the form of increased compensatory participate in tumor immune process. *GPX7* protects cells from ROS production, oxidative stress and oxidative DNA damage. When this threshold is exceeded, it may be involved in tumor development with other tumor cells. On the other hand, the role of *GPX7* in human tumors is dependent on tumor types and stages, *GPX7* may be hijacked by immune cells during tumor progression. In addition, it has been reported that the immune system has a dual role, it antagonizes and promotes tumor development and progression,<sup>42</sup> which also supports our hypothesis. CAFs were reported with fibroblast heterogeneity and plasticity in tumor microenvironment, and have been shown to play multiple roles in tumor development of a tumor. CAFs may also inhibit tumor progression in some circumstances.<sup>43,44</sup> In the present study, we found that *GPX7* was positively correlated with CAFs in 18 tumor types, including LGG, COAD, ESCA, HNSC, PAAD. These findings on *GPX7*-related immune infiltration are of great value for further basic biological research.

TMB is an emerging biomarker that predicts prognosis and the response of cancer patients to immunotherapy. It has been proven effective for some tumors, such as lung cancer,<sup>45</sup> melanoma.<sup>46</sup> Studies have shown that high TMB may promote cancer-testicular antigen expression and inflammation. Patients with high TMB can get a more favorable prognosis after receiving immunotherapy.<sup>47,48</sup> In LGG, TMB is negatively correlated with OS, high TMB may inhibit the immune infiltration of LGG.<sup>49</sup> TMB is an independent prognostic factor for glioma.<sup>50</sup> These research findings were in agreement with the results of this study. Immune checkpoint inhibitor therapy is increasingly being considered as a potential treatment for gliomas. Currently, most immune checkpoint inhibitors are in the Phase I, II and III clinical trial stage in the field of neurosurgery, and the research objects are mostly focused on glioblastoma patients.<sup>51,52</sup> The ideal therapeutic effect of immune checkpoint inhibitors may be more beneficial and more effective for patients with high TMB. This study revealed that the expression of *GPX7* was positively correlated with TMB in LGG. We believe that immune checkpoint inhibitor was expected to be effective on LGG with high expresser of *GPX7*.

Although great efforts have been made in neurosurgery, the prognosis of LGG patients is still very poor. This study explored the effect of *GPX7* combined with chemoradiotherapy on the prognosis of LGG, and revealed that RT may not be a recommended treatment for LGG patients with high *GPX7* expression. And this study reported that high-expressed *GPX7* could predict the sensitivity of TMZ in LGG patients. The above evidence suggests that chemotherapy may be an effective and beneficial treatment for LGG patients with high *GPX7* expression. These findings will be further evaluated and optimized in clinical practice in order to improve the survival prognosis of more LGG patients.

The mechanism of *GPX7* involved in the occurrence and development of glioma is quite complex. Elevated *GPX7* increased the level of glutathione and inhibited lipid peroxidation. A recent study suggested that *GPX7* may be relevant to ferroptosis in glioma. *GPX7* silencing enhances ferroptosis related oxidative stress in glioma cells. Furthermore, it reported that *GPX7* was a direct target of the miR-29 family. *GPX7* restoration can reverse miR-29b mediated enhancement of ferroptosis related oxidative stress.<sup>53</sup> In addition, a bioinformatics study revealed that elevated *GPX7*

is involved in glioma progression through several enriched pathways, including cell cycle pathway, ECM pathway, focal adhesion pathway and toll-like receptor pathway.<sup>32</sup> These findings provided key clues to further study the basic biology of *GPX7* in glioma.

This study has some limitations: First, all parameters and information were obtained from databases, which are limited and incomplete. Second, analytical data on *GPX7* expression were based on mRNA levels, and conclusions of this study were derived from bioinformatics analysis, which lacks experimental data support. Therefore, more studies are needed to verify our results and to investigate the biological functions of *GPX7*, which will make our conclusions to be reliable and generalizable.

## Conclusion

In summary, we elucidate on the expression of *GPX7* across human tumors. *GPX7* is upregulated in multiple tumors. Overexpression of *GPX7* is closely related to poor prognosis in LGG patients. Therefore, *GPX7* is a potential prognostic biomarker for LGG. High-expressed *GPX7* can predict the sensitivity of TMZ in LGG patients. Chemotherapy is a potentially recommended treatment option for LGG patients with high *GPX7* expression. Therefore, this study provided a basis for further evaluation of the role of *GPX7* in clinical tumors.

## Abbreviations

*GPX7*, Glutathione peroxidase-7; TCGA, The Cancer Genome Atlas; GTEx, Genotype-Tissue Expression; GDC, Genomic Data Commons; GEPIA, Gene Expression Profiling Interactive Analysis; HPA, Human Protein Atlas; CGGA, Chinese Glioma Genome Atlas; ROS, Reactive Oxygen Species; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; DSS, disease specific survival; HR, hazard ratio; 95% CI, 95% confidence intervals; ACC, adrenocortical carcinoma; BLCA, bladder urothelial Carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma; TMB, tumor mutational burden; MSI, microsatellite instability; EPIC, Estimating the Proportions of Immune and Cancer cells; CAFs, cancer-associated fibroblasts; TMZ, temozolomide; RT, radiotherapy; IC50, half-maximal inhibitory concentration.

## Data Sharing Statement

The raw data analyzed during the current study are available in the TCGA database (<http://cancergenome.nih.gov>) and the GTEx database (<https://gtexportal.org/home>).

## Ethics Approval and Informed Consent

All data in this study were obtained from public databases, and this study was approved by the Medical Ethics Committee of Xi'an Central Hospital.

## Consent for Publication

All authors gave final approval to submit the manuscript for publication.

## Acknowledgments

We thank those who participated in the preparation and maintenance of the databases used in this study, it is these databases that made our analysis possible. We thank the School of Nursing, Shaanxi University of Chinese Medicine, and Ankang R & D Center of Se-enriched Products for assistance.

## Author Contributions

Qianqian Zhao and Luyu Zhang: the writing of the original manuscript; Yingying Wang, Tianpei Wang, Ye Sun and Jingjing Cao: data collection; Meng Qi, Xiaoping Du and Zengrun Xia: software and data analysis; Rongqiang Zhang and Yin Yang: revision of the original manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was supported by Special R&D Program Project of Chinese Academy of Se-enriched Industry (2020FXZX05-01), Key Research and Development Program of Shaanxi Province (2020SF-076), Research Project from Health Commission of Shaanxi Provincial Government (2018A017), Education Department of Shaanxi Provincial Government (19JS015) and Subject Innovation Team of Shaanxi University of Chinese Medicine(132041933).

## Disclosure

The authors report no conflicts of interest in this work.

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