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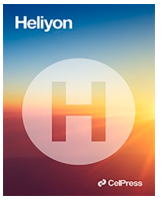

Research article

Selenoprotein GPX3 is a novel prognostic indicator for stomach adenocarcinoma and brain low-grade gliomas: Evidence from an integrative pan-cancer analysis

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A R T I C L E I N F O

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A B S T R A C T

Background: The antioxidant enzyme *GPX3* is a selenoprotein that transports selenium in blood and maintains its levels in peripheral tissues. Aberrant *GPX3* expression is strongly linked to the development of some tumors. However, there is a scarcity of studies examining the pan-cancer expression patterns and prognostic relevance of *GPX3*.

Methods: GPX3 expression levels in normal tissues and multiple tumors were analyzed using TCGA, CCLE, GTEx, UALCAN and HPA databases. Forest plots and KM survival curves were utilized to evaluate the correlation between *GPX3* expression and the outcome of tumor patients. The prognostic value of *GPX3* in LGG was assessed utilizing the CGGA datasets, and that in STAD was tested by TCGA and GEO databases. A nomogram was then constructed to predict OS in STAD using R software. Additionally, the impact of *GPX3* on post-chemoradiotherapy OS in patients with LGG and STAD was evaluated using the KM method. The multiplicative interaction of *GPX3* expression, chemotherapy and radiotherapy on STAD and LGG was analyzed using logistic regression models. The correlation of *GPX3* with the immune infiltration, immune neoantigens and MMR genes were investigated in TCGA cohort.

Results: GPX3 exhibited downregulation across 21 tumor types, including STAD, with its decreased expression significantly associated with improved OS, DFS, PFS and DSS. Conversely, in LGG, low levels of *GPX3* expression were indicative of a poorer prognosis. Univariate and multivariate Cox models further identified *GPX3* as an independent predictor of STAD, and a nomogram based on *GPX3* expression and other independent factors showed high level of predictive accuracy. Moreover, low *GPX3* expression and chemotherapy prolonged the survival of STAD. In LGG patients, chemoradiotherapy, *GPX3* and chemotherapy, and *GPX3* and chemoradiotherapy may improve prognosis. Our observations reveal a notable connection between *GPX3* and immune infiltration, immune neoantigens, and MMR genes.

Conclusions: The variations in *GPX3* expression are linked to the controlling tumor development and could act as a promising biomarker that impacts the prognosis of specific cancers like STAD and LGG.

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1. Introduction

Tumors are characterized by abnormal cell differentiation, uncontrolled proliferation, and loss of contact inhibition [1]. According to the latest estimation by the IARC, approximately 20 million new cases of cancer were diagnosed globally in 2022, leading to the loss of 9.7 million lives [2]. STAD, a prevalent cancer of the gastrointestinal system, arises from the glandular epithelium of the gastric mucosa. With pronounced rates of metastasis and recurrence, it ranks second in terms of mortality compared to other types of cancer [3]. LGG is a rare central nervous system tumor, and its prognosis depends on the mass effect and the affected brain areas [4]. Despite progress in diagnosis, the rising incidence and mortality rates of STAD and LGG emphasize the need to find novel prognostic biomarkers.

Se is a crucial micronutrient necessary for preserving the REDOX process of both normal and tumor cells, serving as a homeostasis regulator [5,6]. Epidemiological and experimental studies have demonstrated that Se exerts beneficial effects on human health and may contribute to maintaining the stability of cellular systems, which in turn inhibits tumor cell differentiation [7,8]. The glutathione peroxidase family comprises eight members (GPX1-GPX8) that primarily catalyze the oxidation of glutathione to reduce peroxides, effectively eliminating ROS produced during cellular oxidative metabolism [9]. Accumulation of ROS in the body can lead to damage to proteins and DNA, ultimately triggering tumorigenesis. *GPX3*, the sole extracellular antioxidant isoenzyme containing selenocysteine, is a significant gene implicated in human antioxidant responses [10]. Research has associated aberrant *GPX3* expression with the development and advancement of various tumors, including melanoma [11], esophageal cancer [12], ovarian cancer [13], colon cancer [14], gastric cancer [15] and other malignancies. However, existing studies have largely focused on individual diseases and genes, and due to variations in research methodologies, sample sizes, and other factors, a consistent conclusion regarding the relationship between *GPX3* and tumors has yet to be reached.

The advancement of gene sequencing technologies has led to the emergence of pan-cancer research, offering a broader perspective in tumor studies and addressing the limitations of individual tumor-focused research [16,17]. This trend represents an inevitable progression in tumor research, expanding the scope and enhancing understanding in this field. This study utilized pan-cancer analysis to investigate the potential correlations between *GPX3* expression and factors such as survival rates, pathological stages, immune infiltration levels, immune neoantigens, and MMR gene status across various cancer types. We validated the diagnostic efficacy and predictive value of *GPX3* for specific tumors using multiple datasets. Additionally, we examined the connection between expression of *GPX3* and the post-radiotherapy and chemotherapy survival outcomes in patients with STAD and LGG. The aforementioned analysis aims to uncover the effect of *GPX3* on the initiation and development of malignant tumors in humans.

2. Materials and methods

2.1. Retrieval of GPX3 expression data

The mRNA sequencing data for 31 normal human tissues were retrieved from the GTEx datasets. *GPX3* expression data of 21 tumor cell lines was extracted from CCLE datasets. Furthermore, RNA-seq data on *GPX3* expression in normal tissues and IHC data on GPX3 protein expression in human normal/tumor tissues were sourced from HPA datasets.

The mRNA sequencing data and clinical details for 20 tumor samples and normal human tissues were sourced from TCGA datasets. Additionally, the datasets from normal tissues in GTEx and 27 cancer tissues from TCGA were integrated to assess the variation in *GPX3* expression levels between tumor and normal tissues [18,19]. The data were normalized by log2 transformation.

Canceromics data from the CPTAC was analyzed through the UALCAN platform [20]. The analysis primarily focused on *GPX3* expression in ovarian cancer, UCEC, colon cancer, clear cell RCC, LUAD and breast cancer. Aberrant GPX3 protein expression levels between cancerous and human normal tissues were evaluated using Z-values, with median protein expression serving as the benchmark. The "Expression DIY" tool within the GEPIA2 platform was utilized to investigate *GPX3* expression across different pathological stages of selected cancers. All data was converted to $\log_2$ (TPM +1), and the corresponding violin plots were constructed [21].

2.2. Prognostic evaluation of GPX3

The "Survival" R software was employed to probe the connection between expression of *GPX3* and the prognosis of 33 cancer types within the TCGA datasets, considering OS, DSS, DFS, and PFS. Subsequently, the optimal cutoff point for *GPX3* expression was determined using the "Maxstat" R software, leading to the categorization of patients into $GPX3^{high}$ and $GPX3^{low}$ groups. Kaplan-Meier curves were generated for patients with STAD (n = 372) and LGG (n = 474), with survival probabilities and prognoses were evaluated in terms of HR values alongside a 95 % CI and log-rank $P < 0.05$.

The CGGA hosts a vast collection of over 2000 brain tumor datasets from Chinese cohorts [22]. In order to verify whether *GPX3* has a cross-racial effects on the survival outcomes of LGG, the mRNAseq_693 and mRNAseq_325 datasets were carefully analyzed. Patients with LGG were sorted into $GPX3^{high}$ and $GPX3^{low}$ groups based on median scores, with a thorough assessment of survival probabilities and prognostic markers. Additionally, the expression profile and diagnostic capacity of *GPX3* in STAD were confirmed using the GSE44861 and GSE29272 datasets from GEO [23,24] and TCGA data.

2.3. Validation of a nomogram model for STAD

A nomogram utilizing *GPX3* was established for predicting the OS of STAD patients. This nomogram's effectiveness was assessed using a concordance index (C-index) ranging from 0.5 (poor) to 1 (perfect), with a higher C-index reflecting improved prognostic precision. Calibration and validation were conducted utilizing the R packages "rms" and "cmprsk" to ensure the nomogram's accuracy [25,26].

2.4. Effect of GPX3 and chemoradiotherapy on the OS of STAD and LGG patients

The influence of *GPX3* expression and treatment regimen on OS in STAD and LGG patients was assessed through TCGA data. Briefly, 351 STAD patients and 534 LGG patients were divided into the radiotherapy (n = 44 and 142), non-radiotherapy (n = 145 and 120), chemotherapy (n = 128 and 223) and non-chemotherapy (n = 34 and 49 respectively) groups, and KM curves were plotted for various subgroups. The "maxsta" tool in R software was employed to compute the optimal risk score threshold, with the sample size parameters set to ensure a minimum of >25 % and a maximum of <75 %.

Multiplicative interaction arises when the combined influence of two or more factors on a disease exceeds the sum of their individual effects [27]. Logistic regression analysis was utilized to assess the multiplicative interaction of *GPX3*, radiotherapy, and chemotherapy on the OS of STAD and LGG, accounting for potential confounding factors. Data from TCGA was utilized, missing values were excluded, and the analysis was conducted via the "interaction" R package.

2.5. Infiltration of immune cells

"Estimate" in R package was utilized to derive ESTIMATE scores for three types of cancers (STAD, LGG, GBM) to assess the immune and stromal constituents within TME. In STAD and LGG, the connection between *GPX3* expression and tumor-infiltrating was evaluated. Moreover, the connection between expression of *GPX3* and immune neoantigens was examined. Mutation data for five MMR genes was acquired from the TCGA datasets, and Pearson correlation analysis was employed to assess the connection between expression of *GPX3* and the mutation levels of MMR genes. A correlation was deemed statistically significant if $R > 0.20$ or $P < 0.05$.

2.6. Statistical analysis

Wilcoxon rank-sum test was used to compare differences between two groups. When exploring the relationship between two continuous variables, either Pearson correlation analysis or Spearman correlation analysis is employed. All statistical analyses and visualizations were performed using either R version 3.5.3 or online web tools. To delve into the correlation between *GPX3* expression and various factors such as prognostic value and immune landscape across different cancers in the TCGA databases, we leveraged SangerBox (http://sangerbox.com/). Notably, all statistical tests were two-tailed, with statistical significance set at $P < 0.05$.

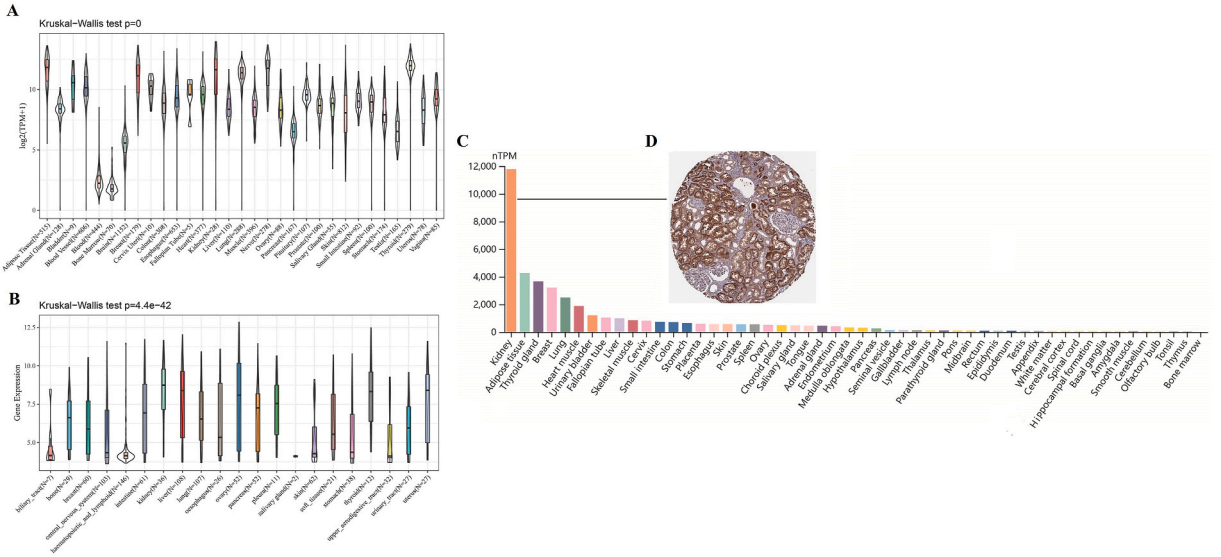

Fig. 1. (A) *GPX3* mRNA levels in human normal tissues. (B) Expression levels of *GPX3* in various tumor cell lines. (C) *GPX3* expression profile in normal human tissues. (D) Representative IHC images showing GPX3 protein expression in normal kidney tissues.

3. Results

3.1. GPX3 is dysregulated in cancers and associated with prognosis

Expression of *GPX3* was analyzed in 31 human tissues, and high expression levels were detected in the adipose tissue, adrenal gland, bladder, blood vessels, etc. (Fig. 1A). Furthermore, *GPX3* was detected in all 21 tumor cell lines analyzed (Fig. 1B). The *GPX3* gene shows significant expression in the Kidney, Adipose tissues, Thyroid gland, and other tissues as demonstrated in Fig. 1C. Representative IHC images of GPX3 protein expression in kidney normal tissues and tumor tissues (prostate cancer, colorectal cancer, lung cancer, liver cancer, breast cancer) are presented in Figs. 1D and 2C. Details of the tissue donors for the IHC analyses are consolidated in Table 1.

We further analyzed *GPX3* mRNA levels in 20 cancers and normal human tissues in TCGA datasets, and found that *GPX3* was downregulated in the tumors compared to the normal human tissues (Fig. 2A). Given the limited number of human normal tissue samples in the TCGA datasets, we combined data from GTEx and TCGA to assess variance in *GPX3* expression among 27 cancer types. As shown in Fig. 2B, *GPX3* expression was lower in CHOL, BLCA, ACC, COAD, BRCA, KICH, CESC, KIRC, OV, HNSC, ESCA, KIRP, LUAD, READ, LUSC, PRAD, SKCM, STAD, TGCT, UCS and THCA tissues compared to the corresponding adjacent tissues, and higher in GBM, LAML and LGG relative to adjacent tissues. Moreover, GPX3 protein expression was identified in prostate cancer, skin cancer, carcinoid, lymphomas, colorectal cancer and renal cancer tissues (Fig. 2D). The protein levels of *GPX3* were notably reduced in clear cell RCC, colon cancer, ovarian cancer, lung adenocarcinoma, breast cancer and UCEC compared to normal tissues (all $P < 0.001$, Fig. S1A). Furthermore, *GPX3* expression was correlated to the pathological staging of BLCA, ACC, KIRP, LIHC, KIRC, READ, THCA and PAAD (all $P < 0.05$, Fig. S1B). Thus, *GPX3* is dysregulated in cancer and may influence disease progression.

The connection between *GPX3* and cancer prognosis was analyzed using TCGA datasets. As depicted in Fig. 3A, $GPX3^{high}$ expression was correlated with poorer OS in STAD, STES, LUSC, READ and COAD, while indicating a more favorable prognosis in GBMLGG, KIRC, PAAD, LGG, and LUAD. Furthermore, $GPX3^{high}$ expression also resulted in worse DSS in STES, STAD, COAD, READ, LUSC and ESCA, but prolonged that in KIRC, GBM, LGG, LUAD and PAAD patients (Fig. 3B). *GPX3* expression also served as a predictor of PFS across 38 tumor types. Diminished *GPX3* expression was linked to extended PFS in individuals with STES, STAD, COAD, and READ, while elevated levels correlated with prolonged PFS in LUAD, GBM, LGG, PRAD, and SKCM-M (Fig. 3C). Furthermore, the reduction in *GPX3* expression was tied to prolonged DFS in STES, STAD, and HNSC, and poor DFS in LUAD (Fig. 3D). The combined results from Cox regression forest plots demonstrated a noteworthy association between *GPX3* levels and DSS, OS and PFS among patients with STAD, STES, and LGG. However, given the limited sample size of STES, KM curve was found that, the OS of the STAD $GPX3^{low}$ group was significantly better than that of the $GPX3^{high}$ group (HR = 1.85, P = 1.7E-4), while the $GPX3^{high}$ group LGG patients had more

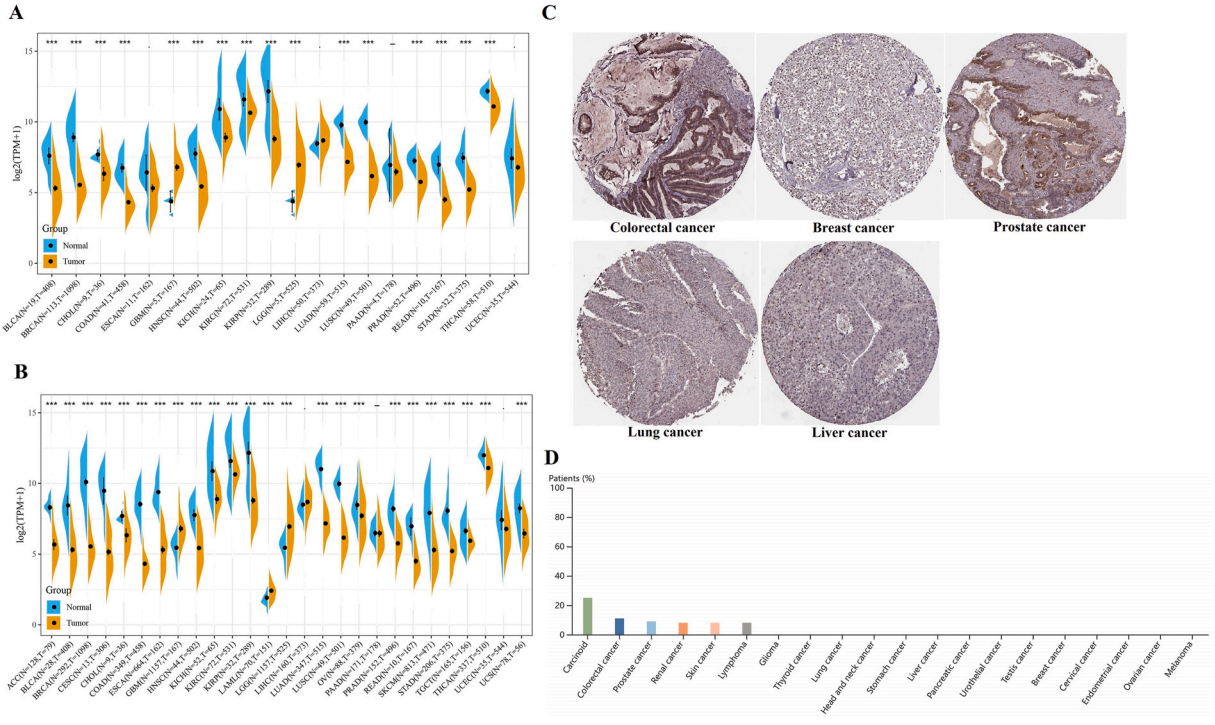

Fig. 2. (A) Differential expression of *GPX3* in normal and tumor tissues in TCGA database. (B) Differential *GPX3* expression in tumor and normal tissues based on the integrated data of GTEx and TCGA databases. (***P < 0.001, **P < 0.01, *P < 0.05) (C) Representative IHC images showing GPX3 protein expression in tumor tissues. (D) GPX3 protein expression in six tumor types.

Table 1
Clinical information of tissue donors for IHC slides.

Protein	Tissue		Histological type	Age	Gender	Location	Quantity	Intensity
GPX3	Colorectal		Adenocarcinoma	78	female	Cytoplasmic/membranous nuclear	>75 %	Moderate
GPX3	Breast		Duct carcinoma	61	female	Cytoplasmic/membranous	>75 %	Weak
GPX3	Prostate		Adenocarcinoma	68	male	Cytoplasmic/membranous	<25 %	Strong
GPX3	Lung		Squamous cell carcinoma	64	male	Nuclear	<25 %	Weak
GPX3	Liver		Carcinoma/Hepatocellular	73	female	Cytoplasmic/membranous	<25 %	Moderate
GPX3	Kidney	glomeruli	Normal tissues	61	male	Cytoplasmic/Membranous nuclear	<25 %	Weak
		tubules					>75 %	Strong

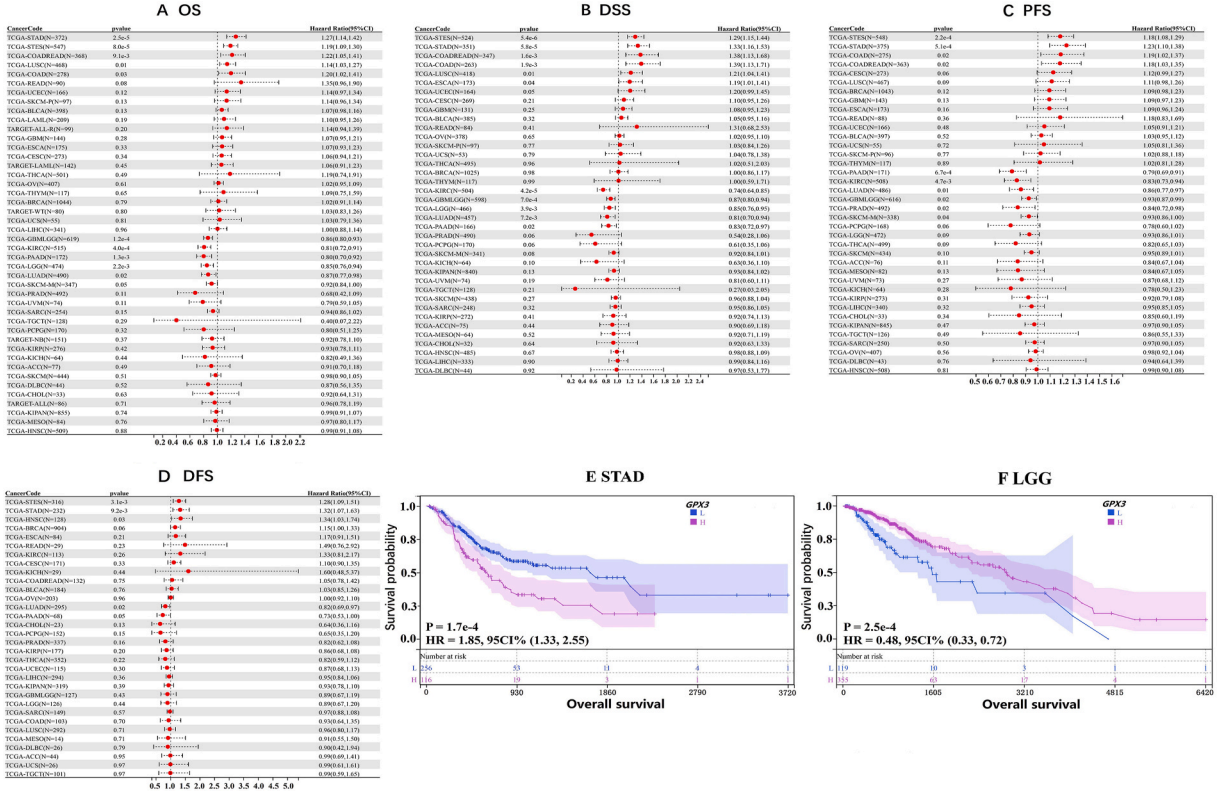

Fig. 3. (A–D) Forest plots illustrating the prognostic significance of *GPX3* across various tumor tissues. (E–F) KM curves of the *GPX3*^{low} and *GPX3*^{high} STAD and LGG patients.

favorable prognosis compared to the *GPX3*^{low} group (HR = 0.48, P = 2.5E-4) (Fig. 3E–F). This study suggests that low *GPX3* expression acts as a protective factor in STAD but a risk factor in LGG. To delve deeper into this intriguing observation, our focus centers on investigating the prognostic significance of *GPX3* in STAD and LGG. Analysis of the CGGA database further confirmed that high *GPX3* expression was beneficial to the prognosis of LGG, and there is specificity in LGG patients of different age and IDH status (Fig. 4A–B).

3.2. *GPX3 expression is an independent prognostic factor in STAD*

Consistent with the results from TCGA datasets, analysis of GEO datasets confirmed that *GPX3* expression in STAD was lower than that in human normal tissues (Fig. 5A). AUC values for the predictive capacity of *GPX3* expression in STAD were 0.8406 (95 % CI: 0.7865–0.8946, P < 0.001) in the GEO datasets and 0.9599 (95 % CI: 0.9464–0.9734, P < 0.001) in the TCGA datasets (Fig. 5B), which indicates that *GPX3* can reliably diagnose STAD. We developed a nomogram utilizing *GPX3* expression level and other prognostic factors (age, gender, pTNM stage, and radiation therapy) to predict the OS of STAD. Nomogram highlighted that the pTNM stage exhibited the most significant impact on prognosis, with age and radiation therapy following suit (Fig. 6A–B). Nomogram was validated by C-index and calibration. The histogram predicted a C-index of 0.69 (95 % CI: 0.627–1; P < 0.001; Fig. 6C), and the calibration curve revealed concordance between the predicted and observed survival rates (Fig. 6D). Thus, the prognostic nomogram can accurately predict the OS in STAD patients.

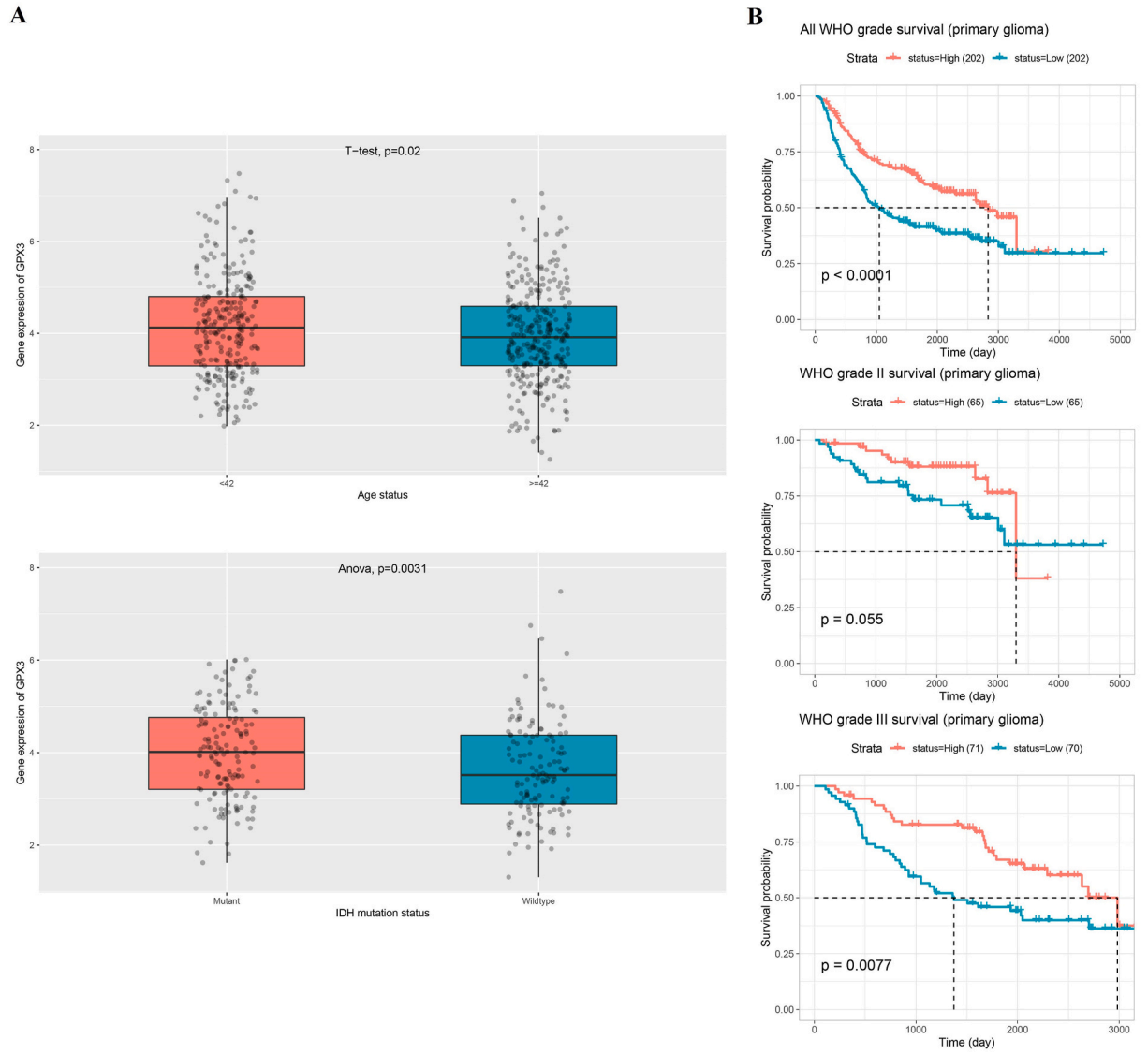

Fig. 4. Relationship between *GPX3* expression and survival outcome in LGG.

3.3. *GPX3 expression and chemoradiotherapy have a multiplicative effect on the OS of STAD and LGG patients*

STAD and LGG patients receiving radiotherapy and chemotherapy were divided into the $GPX3^{high}$ and $GPX3^{low}$ groups, and their survival rates were compared. The OS of $GPX3^{low}$ STAD patients was better compared to that of the $GPX3^{high}$ group (Fig. S2). In contrast, Elevated *GPX3* expression correlated with increased survival likelihood in LGG patients (Fig. S3). Thus, the best prognostic indicators of STAD and LGG were the low and high expression of *GPX3* respectively. We then established multivariable-adjusted associations to explore the multiplicative interactions of *GPX3*, chemotherapy and radiotherapy in STAD and LGG. As shown in Table S2, *GPX3* expression (OR = 1.374, P = 0.002) played a promoting role in STAD patients, which may promote the occurrence of STAD cancer. Conversely, chemotherapy (OR = 0.561, P = 0.026) decreased the mortality rate in STAD patients. As shown in Table S3, *GPX3* expression (OR = 0.881, P = 0.037) was a tumor suppressor for LGG and chemoradiotherapy (OR = 0.548, P = 0.048) decreased the mortality rate of LGG patients, while the combination of both decreased the chances of poor prognosis (OR = 0.906, P = 0.024). These findings can aid in designing more effective preventive and screening measures for STAD and LGG.

3.4. *GPX3 expression and immune infiltration*

GPX3 revealed a positive correlation with the ESTIMATE score in LGG, STAD, and GBM (Fig. 7A). Analysis of the TIMER2 database uncovered a notable positive correlation between *GPX3* expression in STAD and the presence of $CD8^+$ T cells, DCs, macrophages, $CD4^+$

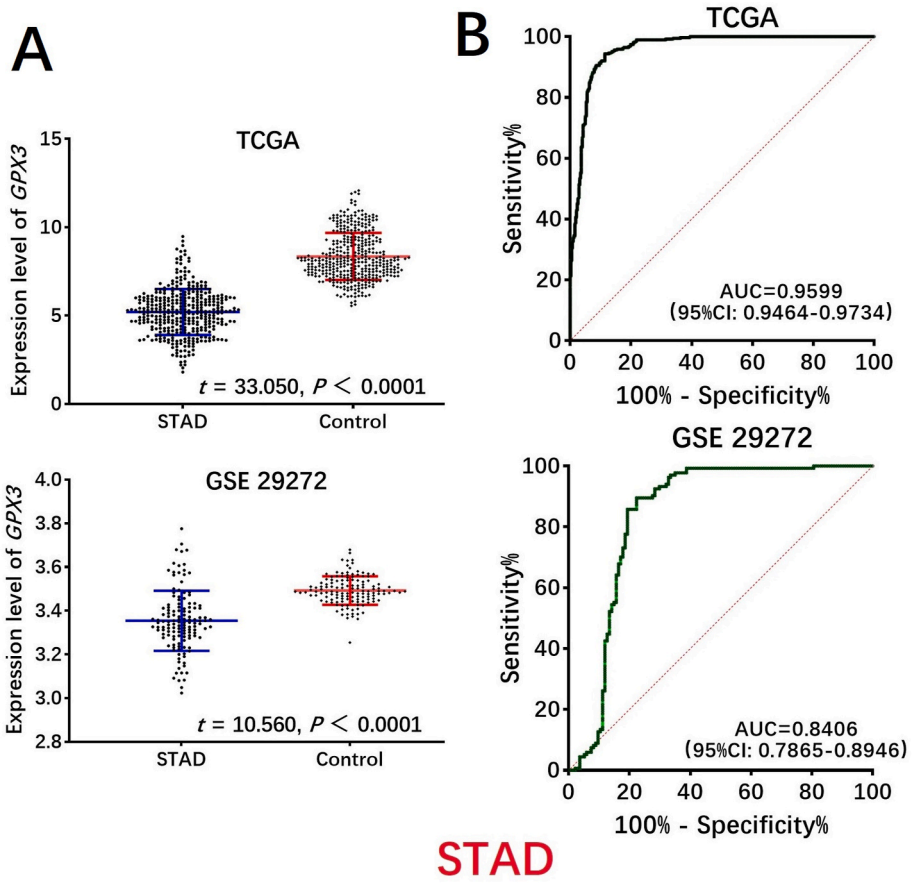

Fig. 5. Independent validation of the distinct expression levels and prognostic relevance of *GPX3* in STAD from GEO and TCGA databases.

T cells and neutrophils, but not with B cells. In contrast, a notable positive association existed between expression of *GPX3* and the infiltration of DCs, $CD4^+$ T cells and neutrophils in LGG. However, no correlation was noted with macrophages and B cells (Fig. 7B). Furthermore, *GPX3* expression was negatively correlated to the number of neoantigens in STAD (R = −0.22, P = 0.0003) but not with LGG (R = 0.0003, P = 0.982) and GBM (R = 0.0005, P = 0.982) (Fig. 7C). Furthermore, to assess the involvement of *GPX3* in tumorigenesis, we investigated the relationship between *GPX3* expression and the level of MMR gene mutations. As illustrated in Fig. 7D, *GPX3* expression level in COAD, BRCA, ESCA, KIRC, GBM, LIHC, OV, LGG, MESO, LUSC, READ, PRAD, SKCM, STAD, SARC and THCA was significantly correlated with the frequency of mutations in 5 MMR genes (MLH1, MSH2, MSH6, EPCAM, PMS2).

4. Discussion

The relationship between Se and cancer remains a contentious topic in medical science. While moderate Se intake can decrease the risk of certain tumors, both inadequate and excessive intake may elevate cancer susceptibility [28,29]. For instance, Se deficiency is linked to higher incidences of colorectal, lung, esophageal, prostate, and liver cancers, whereas Se excess may heighten esophageal cancer risk [30]. *GPX3* serves as a crucial antioxidant enzyme in the body, participating in hydrogen peroxide metabolism by oxidizing glutathione to disulfide form and reducing harmful oxygen radicals [31]. By reducing ROS accumulation, *GPX3* aids in DNA repair and genome stability maintenance. Mechanisms such as gene promoter hypermethylation, DNA copy number loss, and hypoxia-inducible factor-1 can down-regulate *GPX3* gene expression. Reduced *GPX3* expression can lead to DNA damage, genetic alterations, tumor initiation, and enhanced tumor growth and proliferation [32]. Research indicates that reduced *GPX3* expression is linked to breast cancer and a decrease in migration capacity in scratch healing assays [33]. Conversely, high *GPX3* levels, possibly linked to PI3K/AKT activation, may indicate poor survival in gastric adenocarcinoma [34]. *GPX3* expression can also predict lung cancer recurrence post-surgery, serving as a postoperative monitoring biomarker [35]. Even with these findings, the regulation of *GPX3* in most tumors remains unclear, and there is a deficiency of comprehensive analysis on *GPX3* expression across various tumor types. The research leveraged online databases to investigate *GPX3* expression in human tumor and normal tissues, specifically emphasizing the connection between expression of *GPX3* and prognosis in STAD and LGG. The aim was to establish the foundation for using *GPX3* as a potential prognostic indicator for STAD and LGG.

The findings of this study indicated that expression of *GPX3* was evident in both human normal and tumor tissues, with a

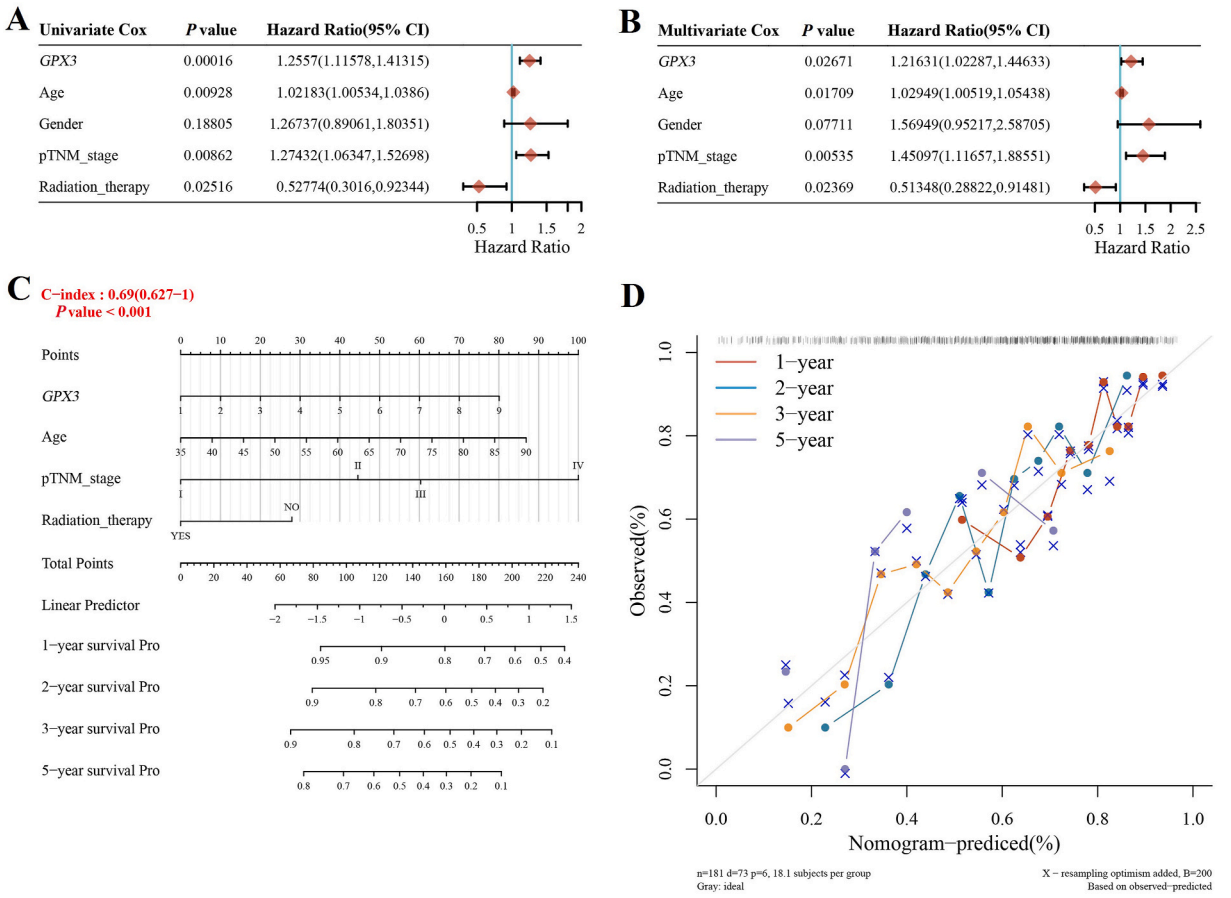

Fig. 6. Predictive nomogram based on *GPX3* expression for STAD. (A, B) Evaluation of clinical parameters and risk scores through univariate and multivariate Cox proportional hazard analyses in STAD patients within the TCGA training cohort. (C) Development of a prognostic nomogram incorporating age, radiation therapy and pTNM stage to estimate survival probabilities at 1, 2, 3, and 5 years. (D) The nomogram's calibration curves predicted survival rates in STAD patients.

statistically notable variance noted in 24 tumor tissues, implying a potential association between *GPX3* and tumor development. Examination of *GPX3* expression and patient outcomes in TCGA tumors uncovered a robust connection between *GPX3* levels and unfavorable prognosis in individuals with LGG and STAD. This implies that *GPX3* could be a vital prognostic indicator in the management of LGG and STAD, hinting at its dual role in cancer. Further analysis of the CGGA datasets affirmed the prognostic relevance of *GPX3* in LGG and revealed higher *GPX3* expression in IDH mutant tumors compared to wild-type tumors, hinting at *GPX3*'s potential involvement in the oncogenic landscape of LGG. Additionally, we identified *GPX3* as a standalone risk factor for STAD and developed a nomogram capable of accurately predicting OS in STAD patients. This innovative nomogram can aid clinicians in evaluating patient prognosis and tailoring treatment strategies accordingly. The MMR pathway plays a crucial role in safeguarding genomic integrity by rectifying DNA replication errors and minimizing chromosomal rearrangements. Any disruption in the MMR genes can serve as a trigger for tumorigenesis [36]. Our analysis delved into the connection between *GPX3* expression and the mutational status of five MMR genes, unveiling a notable positive correlation across 22 tumor types, including ACC and BRCA. Moreover, our research uncovered a correlation between expression of *GPX3* and the infiltration of diverse immune cell subsets in solid tumors, particularly noticeable in STAD and LGG. Neoantigens, which are tumor-specific antigens originating from non-synonymous mutations, are pivotal in eliciting an immune response and influencing the effectiveness of immunotherapy [37]. Interestingly, our results suggested an inverse connection between *GPX3* expression and the abundance of immune neoantigens in STAD.

In the current clinical practice of STAD treatment, precision targeted therapy guided by biomarkers has emerged as a leading research direction [38]. Clinical trials exploring novel targets like Claudin 18.2 [39], HER-2 [40] and FGFR2 [41] are actively ongoing, signifying a significant research surge in this area. Delving deep into biomarkers holds the potential to accurately identify patients and optimize treatment strategies. Se has been highlighted for its role in tumor prevention, sensitization to chemoradiotherapy, and mitigation of chemotherapy side effects [42–45]. Evidence demonstrates that Se can upregulate p21, inhibit MPF, and trigger G2/M phase cell cycle arrest in BRCA, suggesting its ability to stimulate tumor cell apoptosis through various pathways and enhance radiotherapy efficacy within the tumor cell cycle [46]. Selenadiazole derivatives have demonstrated potential in enhancing G2/M phase cell cycle arrest and promoting apoptosis in LIHC during radiotherapy [47]. Wang and colleagues observed Se's capability to

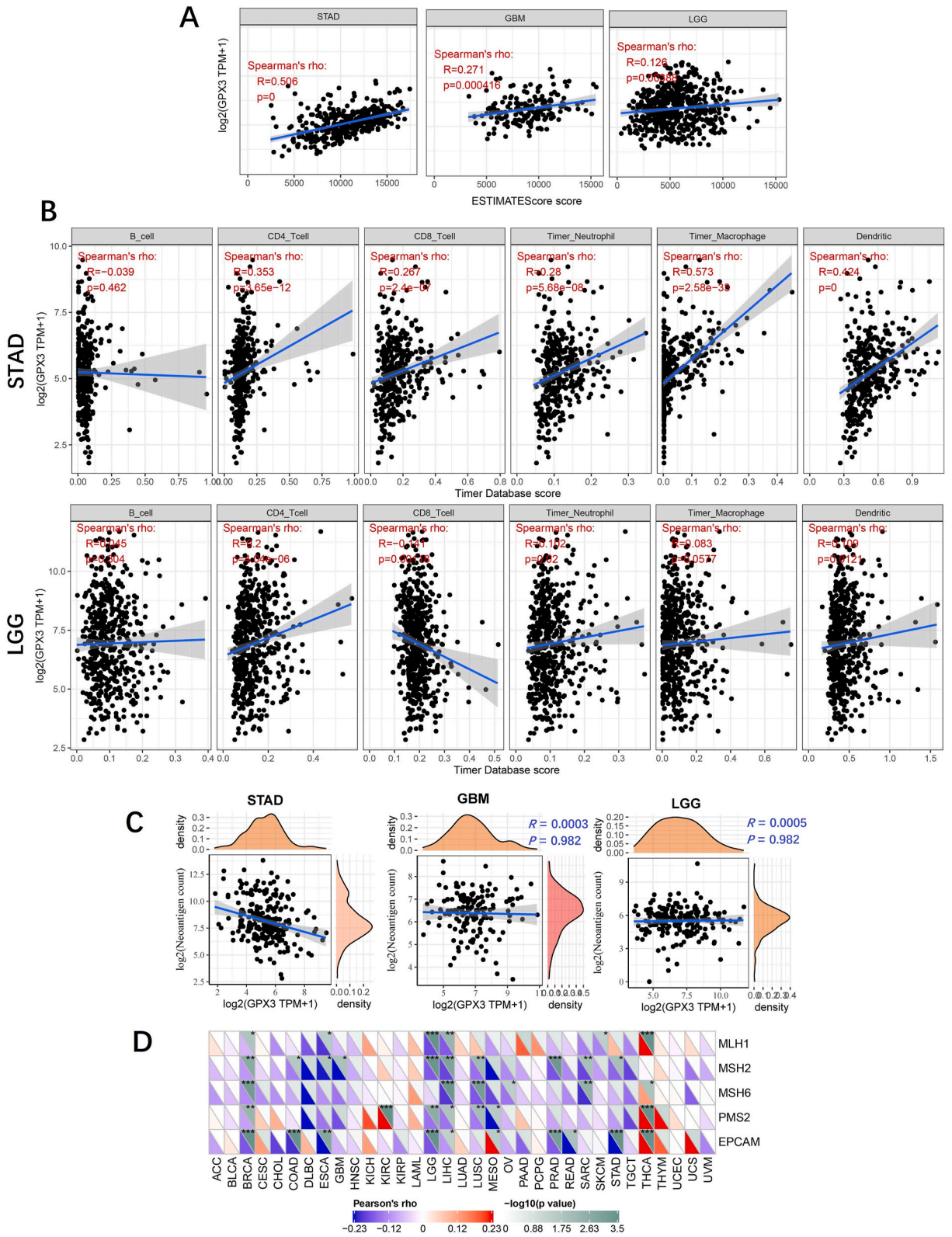

Fig. 7. Role of *GPX3* expression in the immune landscape of STAD and LGG. Association between *GPX3* expression and (A) ESTIMATE Score, (B) immune cells (C) immune neoantigens, and (D) MMR gene mutations.

enhance tumor cell chemotherapy sensitivity by modulating Bcl-2/Bax expression [48]. We scrutinized the effects of radiotherapy and/or chemotherapy on the survival rates of STAD and LGG. As previously discussed, low *GPX3* expression prolonged STAD patient survival but exerted a suppressive effect in LGG. Multiplicative interaction models suggested that *GPX3* had a minimal effect on STAD, LGG patient survival, with chemotherapy yielding improved clinical results. Contrarily, in LGG, combining chemoradiotherapy with *GPX3*, *GPX3* and chemotherapy, as well as high *GPX3* expression all enhanced patient outcomes. The expression of *GPX3* may have a potential association with the prognosis for survival in STAD, LGG patients, suggesting that the prospects related to its targeted therapy are worth attention. Although there are sound justifications for clinical trials assessing the impact of Se supplements on cancer chemoprevention, recent evaluations of trial data have revealed minimal advantages of Se supplements in this context [49]. In addition, there is evidence suggesting that Se supplementation could potentially have negative consequences. For example, studies have shown a notable link between Se supplementation and a higher likelihood of aggressive prostate cancer [50]. Further comprehensive and controlled research is necessary to clarify the effectiveness of Se supplementation in cancer prevention strategies. Therefore, in clinical practice, to maximize the benefits of selenoproteins, it is crucial to determine whether Se supplementation or restriction is more suitable based on the specific tumor type. This issue is expected to become a key focus of clinical research.

Differences in the levels of *GPX3* mRNA and protein expression are evident among various tumor types. Selenium and selenoproteins exhibit dual regulatory functions in the initiation, progression, and therapy of tumors, with levels that are either too high or too low being detrimental to certain types of tumors. Therefore, when utilizing Se to control tumors, we must take these facts into consideration, as it is a complex process. Se in cancer treatment is not universally applicable, and individual analysis is required for each case. Tailored intervention strategies based on specific tumor types, whether through Se supplementation or restriction of Se intake, are essential. In future research, we will focus on individualized Se status and *GPX3* expression analysis, exploring the correlation between individual Se status, Se intake, and changes in Se supply in tumor tissues. If the expression of the GPX3 protein can be altered through nutrition or Se supplementation, this may present new opportunities, potential risks, and intriguing therapeutic prospects.

This study has several limitations. Firstly, the mRNA expression data sample size for certain tumor types is insufficient to ascertain the role of *GPX3* in these tumors. Secondly, the study findings rely on the analysis of public datasets and have not undergone validation through in vitro or vivo experiments. Additionally, there is a lack of clinical data on serum Se and selenoproteins, such as the overall Se status of patients. Lastly, causal relationships cannot be determined from the results of the article.

5. Conclusion

GPX3 exhibits abnormal expression in 24 types of human cancers. Low *GPX3* expression is linked to higher OS rates in STAD patients but the opposite holds true for LGG patients. *GPX3* holds potential in predicting the response of STAD and LGG patients to immune therapy and chemotherapy. Based on existing research findings, the author speculates that *GPX3* likely exerts a notable influence on the progression of STAD and LGG, possibly serving as a prognostic marker for these cancers. However, further exploration is required to gather more evidence in support of this hypothesis.

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Data availability statement

Data included in article/supp. material/referenced in article.

Availability of data and materials

All data in the article are sourced from publicly available databases. TCGA data set can be obtained from the following website: http://cancergenome.nih.gov. GTEx data set can be obtained from the following website: http://commonfund.nih.gov/GTEx/. CCLE data set can be obtained from the following website: https://portals.broadinstitute.org/ccle/. HPA data set can be obtained from the following website: https://www.proteinatlas.org/. UALCAN data set can be obtained from the following website: http://ualcan.path.uab.edu/analysis-prot.html. GEPIA2 data set can be obtained from the following website: http://gepia2.cancer-pku.cn/#index. CGGA data set can be obtained from the following website: http://www.cgga.org.cn/. GEO data set can be obtained from the following website: https://www.ncbi.nlm.nih.gov/geo/.

CRediT authorship contribution statement

Yuetong Wang: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Guotao Fu:** Investigation. **Xueqin Chen:** Software, Investigation. **Zengrun Xia:** Formal analysis. **Meng Qi:** Validation. **Xiaoping Du:** Formal analysis. **Kun Liu:** Data curation. **Qiling Liu:** Validation. **Na Sun:** Data curation. **Chuandao Shi:** Validation. **Kai Qu:** Supervision, Project administration. **Rongqiang Zhang:** Writing – review & editing, Software, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32271.

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Abbreviations

GPX3: glutathione peroxidase 3
LGG: Brain lower grade glioma
STAD: Stomach Adenocarcinoma
OS: overall survival
MMR: DNA mismatch repair
DFS: disease-free survival
DSS: disease-specific survival
PFS: progression-free survival
IARC: International Agency for Research on Cancer
Se: Selenium
ROS: Reactive Oxygen Species
IHC: immunohistochemistry
CPTAC: Clinical Proteomics Tumor Analysis Consortium
TME: tumor microenvironment
DCs: dendritic cells
ACC: Adrenocortical Carcinoma
BRCA: Breast Invasive Carcinoma
BLCA: Bladder Urothelial Carcinoma
CHOL:: Cholangiocarcinoma
CESC: Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma
COAD: Colon Adenocarcinoma
ESCA: Esophageal Carcinoma
KICH: Kidney Chromophobe
KIRC: Kidney Renal Clear Cell Carcinoma
HNSC: Head and Neck Squamous Cell Carcinoma
KIRP: Kidney Renal Papillary Cell Carcinoma
LUSC:: Lung Squamous Cell Carcinoma
LUAD: Lung Adenocarcinoma
OV: Ovarian Serous Cystadenocarcinoma
READ: Rectum Adenocarcinoma
PRAD: Prostate Adenocarcinoma

SKCM: Skin Cutaneous Melanoma
TGCT: Testicular Germ Cell Tumors
UCS:: Uterine Carcinosarcoma
THCA: Thyroid Carcinoma
GBM: Glioblastoma Multiforme
LAML:: Acute Myeloid Leukemia
UCEC: Uterine Corpus Endometrial Carcinoma
LIHC: Liver Hepatocellular Carcinoma
PAAD: Pancreatic Adenocarcinoma
AUC: area under the ROC curve
MESO: Mesothelioma
SARC: Sarcoma