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SLC25A11 serves as a novel prognostic biomarker in liver cancer

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Liver cancer is a disease with high mortality; it is often diagnosed at intermediate and advanced stages and has a high recurrence rate. ROS restriction and adequate energy supply play significant roles in liver cancer. SLC25A11, a member of the malate-aspartate shuttle (MAS), regulates electroneutral exchange between 2-oxoglutarate and other dicarboxylates. It transports glutathione (GSH) from the cytoplasm into mitochondria to maintain GSH levels to limit ROS production. Moreover, SLC25A11 is essential for ATP generation in cancers as it regulates NADH transportation from the cytoplasm to mitochondria. The purpose of this research was to investigate the prognostic value of SLC25A11 in liver cancer. The Cancer Genome Atlas database was used to analyze the levels of SLC25A11 in liver cancer. Fisher's exact and chi-square tests were used to evaluate the relationship between SLC25A11 expression and clinical characteristics. Finally, we explored the value of SLC25A11 in prognosis by Cox analysis and Kaplan-Meier curves. Our results revealed that SLC25A11 was downregulated in liver cancer compared to normal controls. Low expression of SLC25A11 was associated with clinical stage, vital status, histologic grade, overall survival (OS) and relapse-free survival (RFS). Liver cancer patients with low SLC25A11 expression had shorter OS and RFS than patients with high SLC25A11 expression. Multivariate analysis showed that the expression of SLC25A11 was an independent predictor of RFS and OS. In conclusion, this study identified that SLC25A11 serves as a new prognostic marker for liver cancer.

Liver cancer is a key cause of cancer-related mortality, accounting for 8.2% of total cancer deaths¹. Most liver cancer patients are diagnosed at intermediate and late stages and cannot receive curative therapies, which contributes to the low survival rates and high recurrence rates of patients. With surveillance of identifiable high-risk patients and surgical intervention for early-stage patients, the 5-year survival rate has increased to 26%². However, the recurrence rate of HCC is still over 70% at 5 years even after resection³. Therefore, it is essential to find an early screening strategy for diagnosis and prognosis prediction in liver cancer. Unfortunately, current screening markers are unsatisfactory due to their poor sensitivity and specificity. Reliable biomarkers for to improve diagnosis and to predict prognosis after treatment are urgently required.

SLC25A11 is also known as oxoglutarate carrier (OGC), which regulates electroneutral exchange between 2-oxoglutarate and some dicarboxylates⁴. It transports glutathione (GSH) from the cytoplasm to the mitochondrial matrix together with a dicarboxylate carrier (DIC; SLC25A10)⁵. Because of the importance of the GSH system in mitochondria, the regulation of the mitochondrial glutathione (mtGSH) pool can influence the metabolic disorders caused by mitochondrial dysfunction, such as diabetic nephropathy, aging and cancer^{6,7}. Moreover, as a member of the malate-aspartate shuttle (MAS) family, SLC25A11 is essential for ATP generation by NADH transportation from the cytoplasm to mitochondria⁸. Therefore, these studies suggest that SLC25A11 is a key factor in the transportation of NADH and GSH from the cytoplasm into mitochondria in cancer.

Recent studies suggest that SLC25A11 plays a role in the formation of non-small-cell lung cancer (NSCLC)⁸. In addition, it promotes liver cancer by maintaining mtGSH under cholesterol loading⁹. However, the prognostic significance of SLC25A11 expression in liver cancer has not yet been determined. The diagnostic value of SLC25A11 has been evaluated by exploring the correlations between SLC25A11 expression and clinical features from the TCGA. Our results demonstrated that SLC25A11 could be a reliable marker for diagnosis and a predictor of prognosis in liver cancer.

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Parameter	Variables	N	SLC25A11 expression				χ^2	P value
			High	%	Low	%		
Age	<55	117	54	27.84	63	35.39	2.122	0.145
	\geq 55	255	140	72.16	115	64.61		
Sex	Female	121	64	32.82	57	32.02	0.003	0.957
	Male	252	131	67.18	121	67.98		
Histological type	Fibrolamellar carcinoma	3	3	1.54	0	0.00	2.840	0.343
	Hepatocellular carcinoma	363	188	96.41	175	98.31		
	Hepatocholangiocarcinoma (mixed)	7	4	2.05	3	1.69		
Histologic grade	G1	55	35	18.23	20	11.36	9.400	0.023
	G2	178	100	52.08	78	44.32		
	G3	123	52	27.08	71	40.34		
	G4	12	5	2.60	7	3.98		
Stage	I	172	100	55.25	72	42.86	8.161	0.039
	II	87	41	22.65	46	27.38		
	III	85	36	19.89	49	29.17		
	IV	5	4	2.21	1	0.60		
T classification	T1	182	107	55.44	75	42.13	7.691	0.081
	T2	95	44	22.80	51	28.65		
	T3	80	37	19.17	43	24.16		
	T4	13	5	2.59	8	4.49		
	TX	1	0	0.00	1	0.56		
N classification	N0	253	130	66.67	123	69.49	1.797	0.404
	N1	4	1	0.51	3	1.69		
	NX	115	64	32.82	51	28.81		
M classification	M0	267	138	70.77	129	72.47	0.883	0.756
	M1	4	3	1.54	1	0.56		
	MX	102	54	27.69	48	26.97		
Radiation therapy	NO	340	177	97.25	163	98.19	0.051	0.821
	YES	8	5	2.75	3	1.81		
Residual tumor	R0	326	174	91.58	152	86.36	4.121	0.210
	R1	17	7	3.68	10	5.68		
	R2	1	1	0.53	0	0.00		
	RX	22	8	4.21	14	7.95		
Vital status	Deceased	130	56	28.72	74	41.57	6.218	0.013
	Living	243	139	71.28	104	58.43		

Table 1. Relationship between the clinical features of liver cancer and SLC25A11 expression.

Result

Characteristics of patients in this study. Gene expression data and the clinical data were collected from the TCGA and organized. Clinical characteristics included age, sex, TNM classification, residual tumor status, radiation therapy, overall survival and relapse-free survival (Table 1).

Low SLC25A11 expression in liver cancer. The analysis of SLC25A11 was conducted to compare the difference in SLC25A11 expression between primary HCC tissues and normal liver tissue via box plots (Fig. 1). The results showed that SLC25A11 mRNA was downregulated in liver cancer ($P = 0.0019$), which was also verified by the GSE54236 and HCCDB databases (Fig. 1). In addition, we compared SLC25A11 mRNA expression among different clinical characteristics, including stage, histologic grade, TNM classification, histological type, sample type and vital status, and found that SLC25A11 mRNA expression was significantly different when patients were grouped by stage ($P = 0.044$) and histologic grade ($P = 0.096$).

The diagnostic value of SLC25A11. The diagnostic value of SLC25A11 was evaluated by ROC curve analysis using data from the TCGA. The area below the ROC curve (AUC) was 0.635, suggesting the modest diagnostic value of SLC25A11 (Fig. 2). Subgroup analysis revealed the diagnostic value in different stages of liver cancer with AUC values of 0.593, 0.668, 0.696, and 0.588 for stage I, stage II, stage III, and stage IV, respectively (Fig. 2).

Correlations between SLC25A11 and clinical features with liver cancer. After dividing the patients into low/high SLC25A11 mRNA groups according to the threshold value determined by the ROC curve, the relationships between clinical features and SLC25A11 expression were analyzed (Table 1). Histologic grade ($P = 0.0244$), clinical stage ($P = 0.0428$) and vital status ($P = 0.0126$) were significantly correlated with SLC25A11 expression.

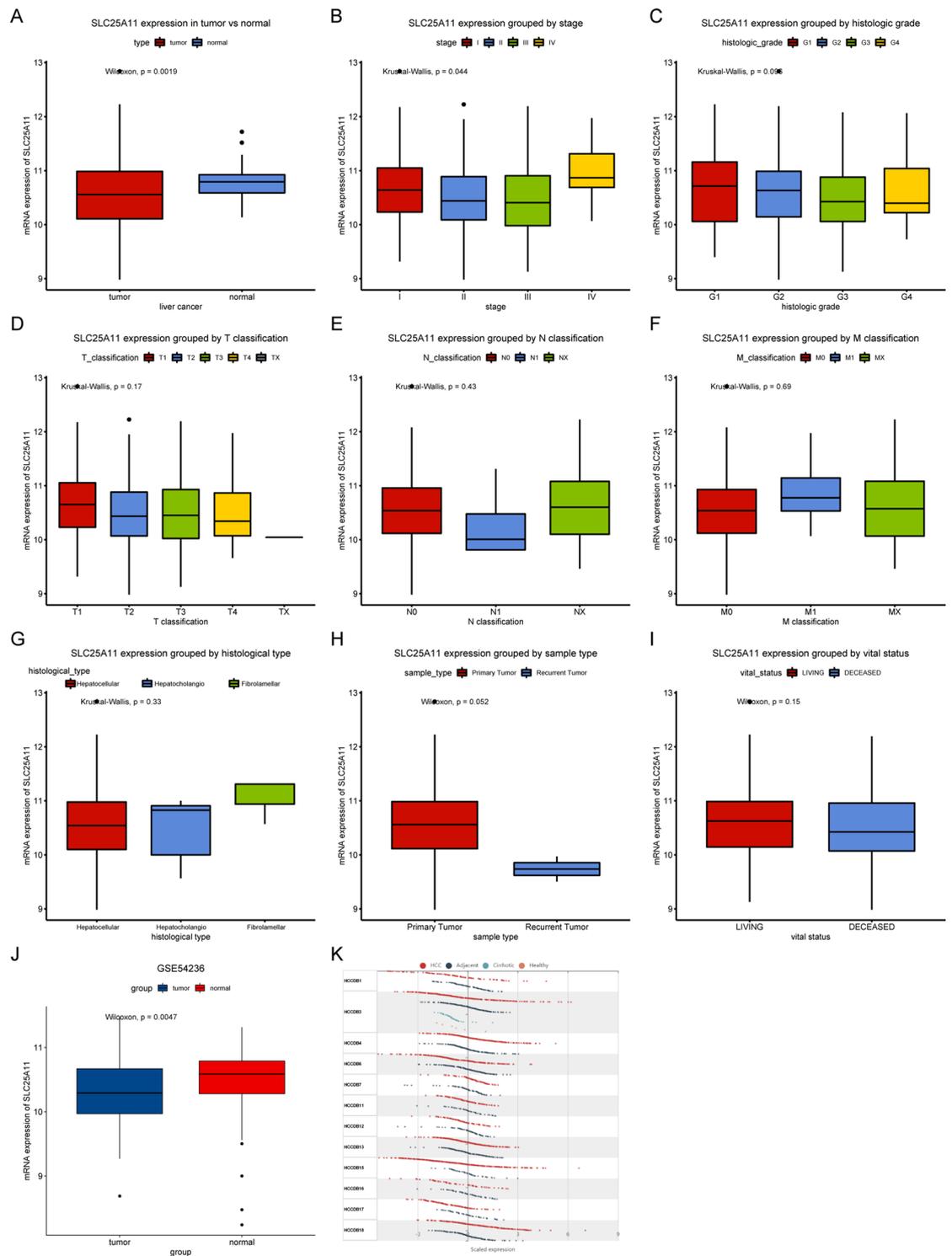


Figure 1. SLC25A11 expression in liver cancer. SLC25A11 expression in liver cancer tissues was compared with that in normal tissues. Subgroup analysis of SLC25A11 according to stage, histologic grade, TNM classification, histological type, sample type, and vital status. Verification in the GSE54236 and HCCDB databases.

Low SLC25A11 predicts poor prognosis of OS and RFS. Kaplan-Meier survival curves were constructed to explore the prognostic value of SLC25A11 in OS. The results showed that low expression of SLC25A11 was related to worse OS ($P = 0.0088$; Fig. 3). In addition, a survival curve was constructed to test the prognostic value of SLC25A11 in RFS. The results showed that low SLC25A11 expression was associated with poorer RFS than high SLC25A11 expression ($P = 0.002$; Fig. 3), which was also confirmed by using the ICGC and GSE54236 databases (Fig. 3).

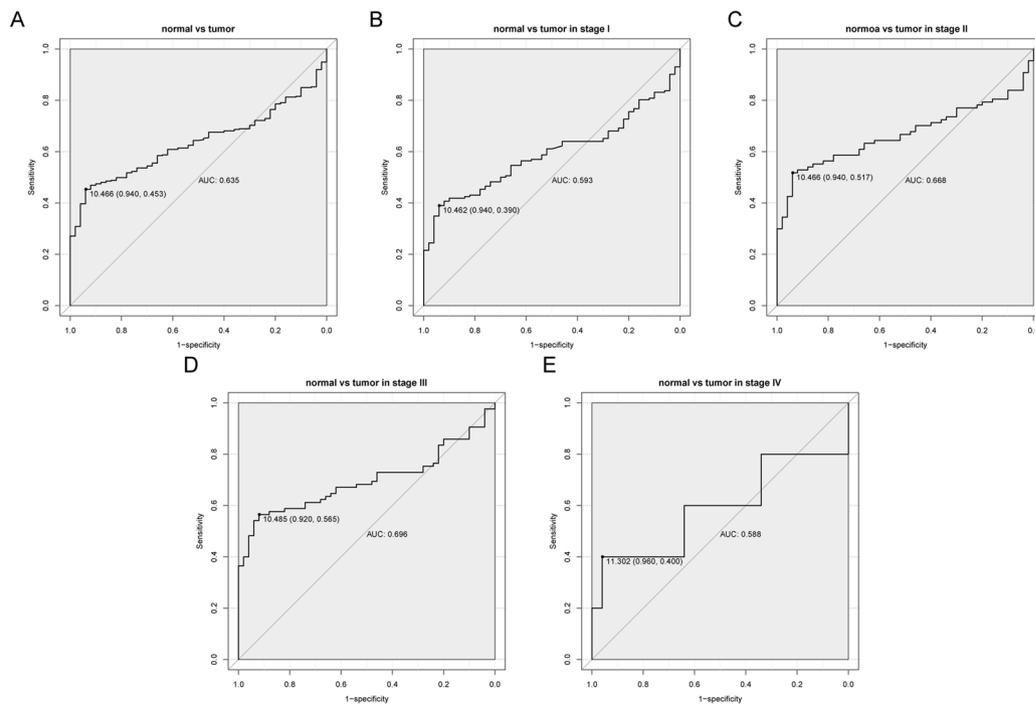


Figure 2. The diagnostic value of SLC25A11 mRNA expression in liver cancer. **(A)** The ROC curve of SLC25A11 expression in liver cancer tissues was compared with that of normal tissues. **(B–E)** Subgroup analysis for stage I, II, III, and IV liver cancer.

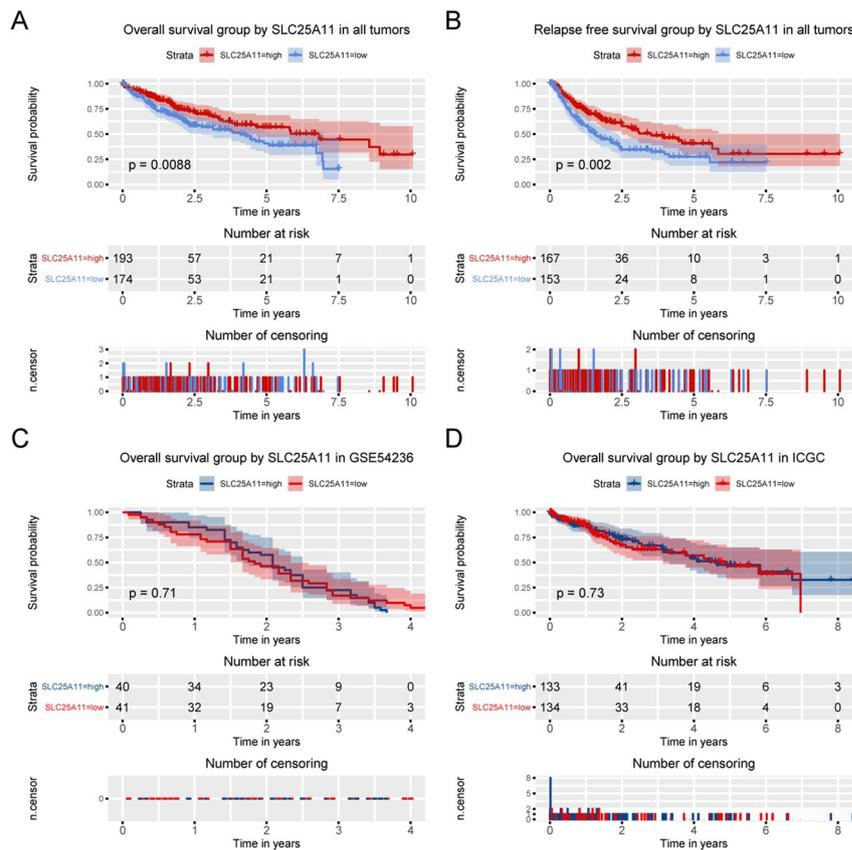


Figure 3. Kaplan-Meier curves for OS and RFS according to SLC25A11 expression in liver cancer. Survival analysis of OS and RFS was performed based on Kaplan-Meier curves in TCGA database, GSE54236 and HCCDB database.

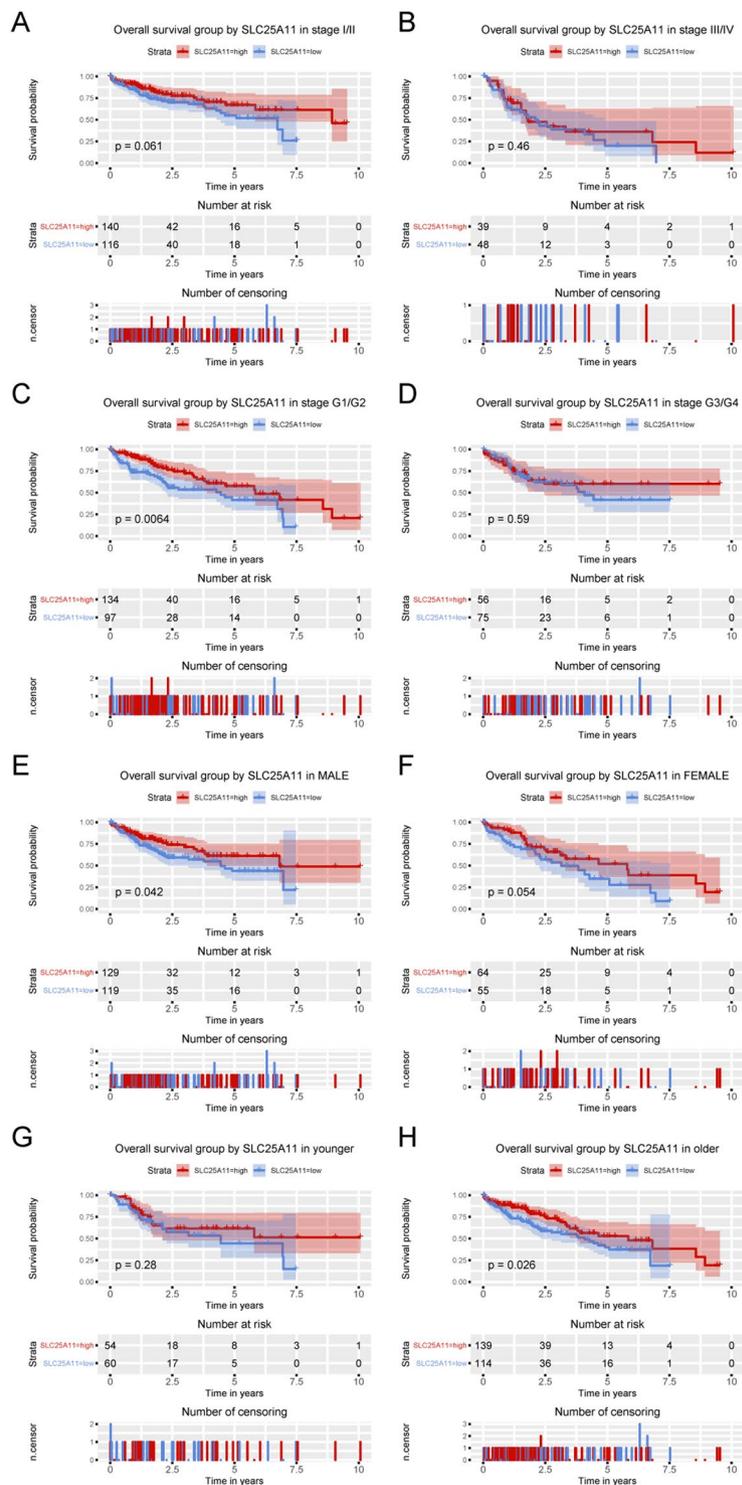


Figure 4. Kaplan-Meier curves for OS according to SLC25A11 expression in liver cancer. Subgroup analysis of OS was performed based on Kaplan-Meier curves according to clinical stage, histological grade, sex and age.

Subgroup analysis revealed the prognostic value of SLC25A11 in terms of OS. Subgroup analysis revealed that the low expression of SLC25A11 was correlated with poor OS in grade G1 and G2 patients ($P = 0.0061$), older patients ($P = 0.026$), and male patients ($P = 0.042$) (Fig. 4).

Subgroup analysis revealed the prognostic value of SLC25A11 in terms of RFS. Subgroup analysis revealed that low expression of SLC25A11 was correlated with poor OS in stage I and II patients ($P = 0.0091$), G1 and G2 patients ($P = 0.027$), G3 and G4 patients ($P = 0.021$), male patients ($P = 0.0011$) and older patients ($P = 0.0021$) (Fig. 5).

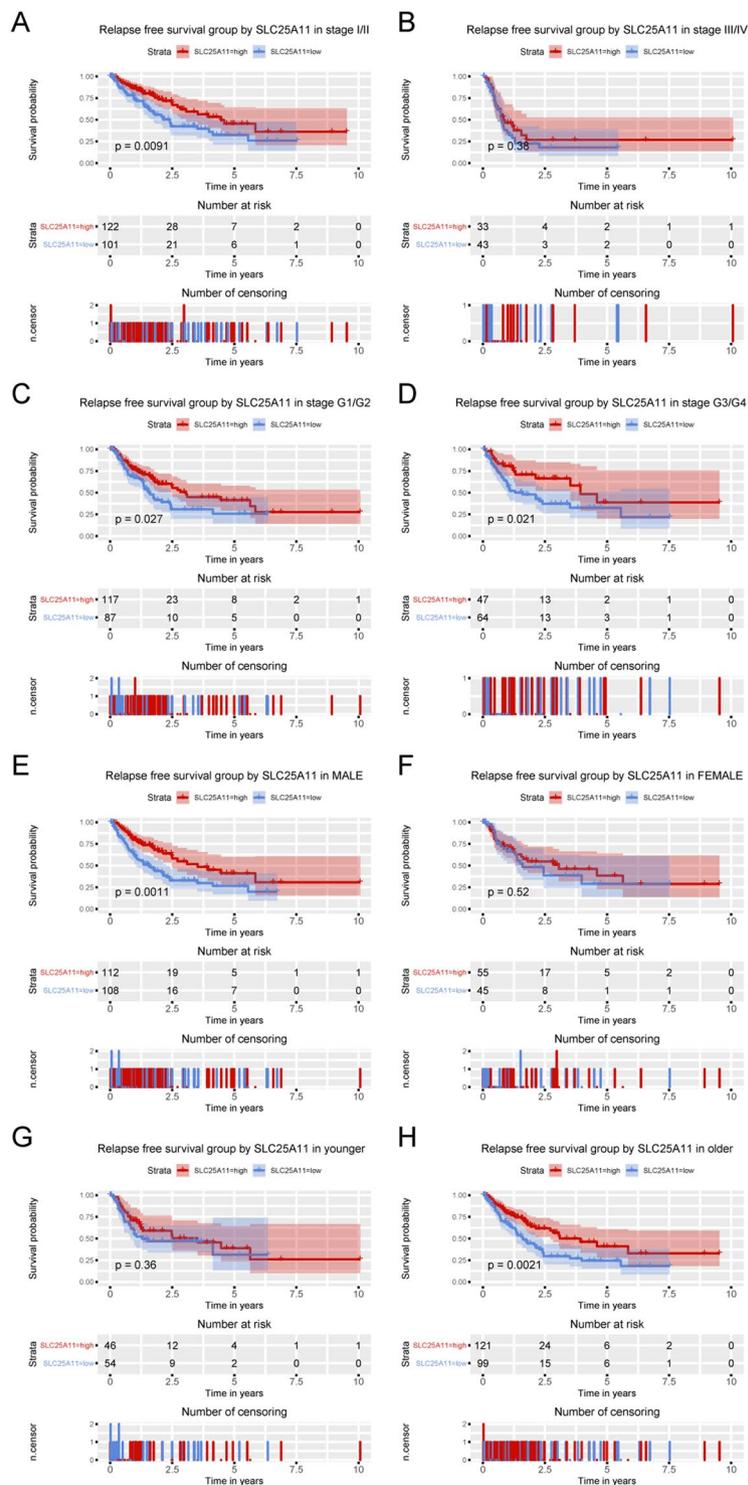


Figure 5. Kaplan-Meier curves for RFS according to SLC25A11 expression in liver cancer. Subgroup analysis of RFS was performed based on Kaplan-Meier curves according to clinical stage, histological grade, sex and age.

Low SLC25A11 is an independent predictor of OS. Univariate Cox analysis identified the potential OS-related variables, including the stage, T classification, residual tumor status and SLC25A11. Multivariate Cox analyses showed that SLC25A11 expression (HR value: 1.526, 95% CI: 1.072–2.172, $P = 0.019$), residual tumor status (HR value: 1.410, 95% CI: 1.103–1.801, $P = 0.006$), and T classification (HR value: 1.835, 95% CI: 1.458–2.310, $P < 0.001$) were independent predictors of poor OS (Fig. 6).

Low SLC25A11 is an independent predictor of RFS. Univariate Cox analysis identified the potential RFS-related variables, including the stage, T classification, residual tumor status and SLC25A11. Multivariate

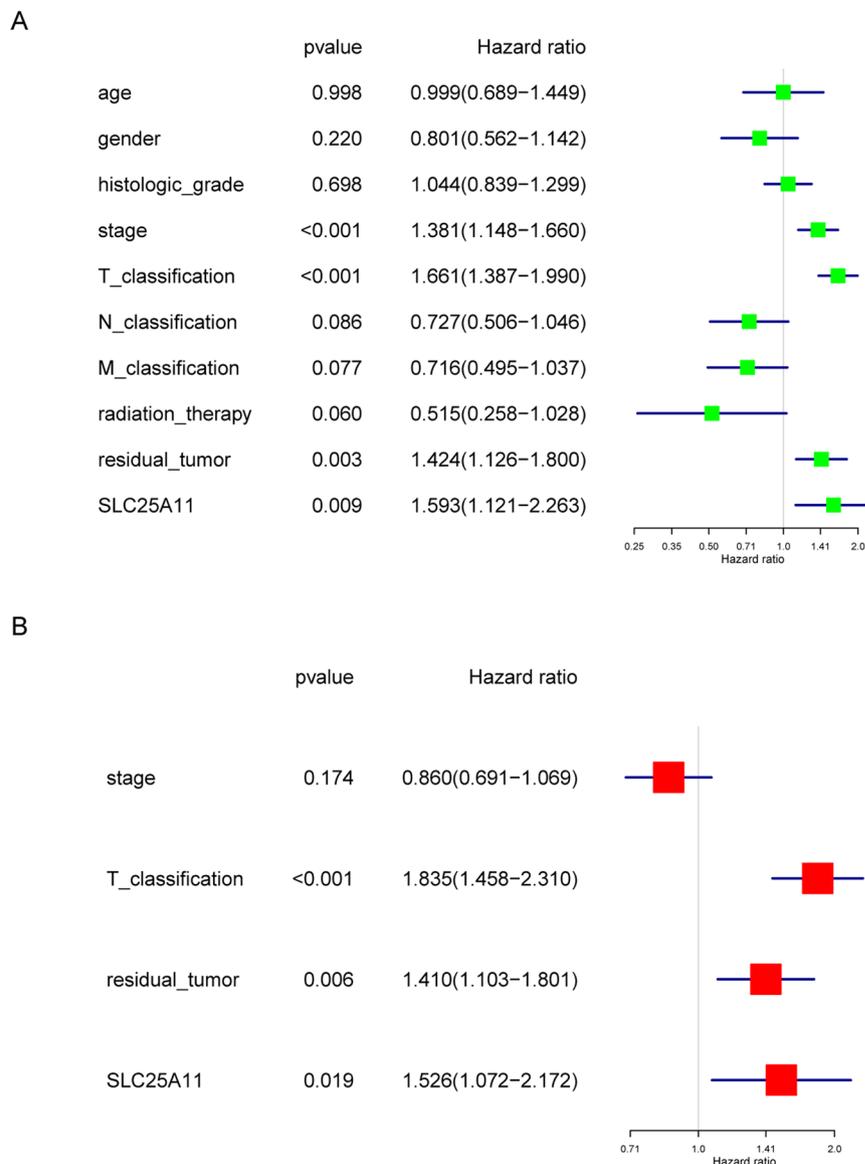


Figure 6. Cox model of OS among liver cancer patients. Univariate and multivariate analysis of the correlation of SLC25A11 expression with OS among liver cancer patients.

Cox analyses showed that SLC25A11 expression (HR value: 1.604, 95% CI: 1.145–2.246, $P = 0.006$), residual tumor status (HR value: 1.300, 95% CI: 1.021–1.655, $P = 0.034$), and T classification (HR value: 1.671, 95% CI: 1.287–2.169, $P < 0.001$) were independent predictors of poor RFS (Fig. 7).

Discussion

Among cancers worldwide, liver cancer has one of the worst prognoses. Many studies have investigated novel prognostic biomarkers in different types of cancer^{10–26}. In this study, we demonstrated that SLC25A11 was low expressed in liver cancer by analyzing data from the TCGA. Low expression of SLC25A11 is related to poor prognosis. Both univariate and multivariate Cox analyses revealed that SLC25A11 played an important role in OS and RFS, which means that SLC25A11 is a novel independent prognostic factor in liver cancer.

In recent years, high SLC25A11 has been found in NSCLC and melanoma⁸. However, we found that SLC25A11 was expressed at low levels in liver cancer. ROC analysis suggested that SLC25A11 could be regarded as a marker in the diagnosis and prognosis of liver cancer. Moreover, we observed that histologic grade, clinical stage, and survival status were related to SLC25A11 expression, which confirmed the significance of this molecule.

SLC25A11, a member of the malate-aspartate shuttle (MAS), regulates the shuttling of 2-oxoglutarate by dicarboxylates from different tissues and cells using various methods^{27–29}. These studies also provide evidence that SLC25A11 is a GSH carrier. In addition, SLC25A11 induction is a key strategy for maintaining mtGSH levels to limit ROS production in HCC⁹. Based on the findings that SLC25A11 expression is associated with clinical stage and histologic grade in liver cancer, we postulate that by stabilizing the mitochondrial membrane

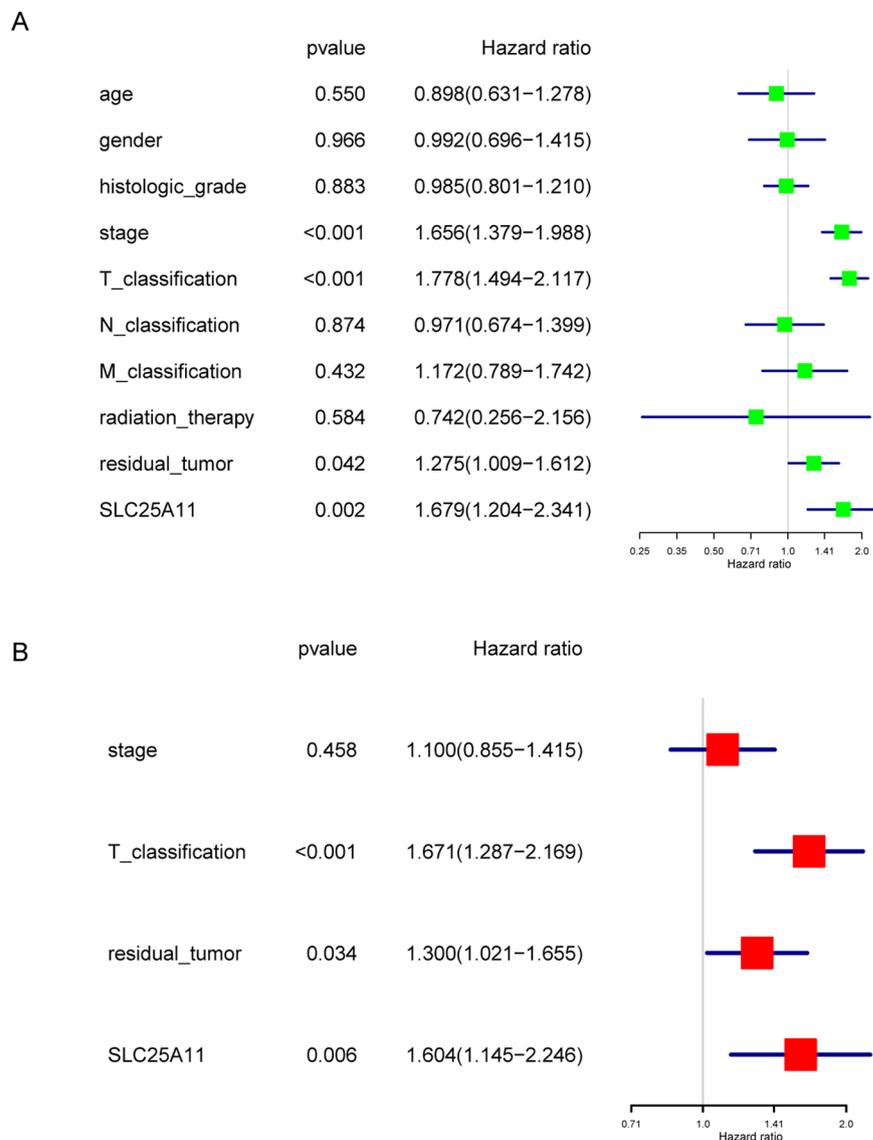


Figure 7. Cox model of RFS among liver cancer patients. Univariate and multivariate analysis of the correlation of SLC25A11 expression with RFS among liver cancer patients.

and maintaining sufficient mtGSH to withstand hypoxia-induced ROS production and cell apoptosis, SLC25A11 improves cell growth and tumor progression.

As one of the characteristics of cancer, fast growing cancer cells requires more ATP than normal cells. Because cancer cells rely mainly on glycolysis for energy, they maintain high mitochondrial oxidative phosphorylation for ATP generation and survival³⁰. SLC25A11 has been proven to be a crucial transporter of NADH from the cytoplasm to mitochondria in the ATP production process, especially in cancer cells. Therefore, the association of the expression of SLC25A11 with poor survival may be due to the effect of SLC25A11 on tumor energy metabolism. This implies that SLC25A11 is necessary for embryogenesis but not for the proliferation of differentiated cells, which suggests that it can be a good marker for cancer.

To our knowledge, our research is the first to show the significant role of SLC25A11 in the prognosis of liver cancer by mining the TCGA database. We found that SLC25A11 could be regarded as a prognostic factor for poor survival in liver cancer. However, the total number of patients evaluated is a limitation of our research. There was no significant correlation between SLC25A11 expression and overall survival in ICGC and the GSE54236 database in Fig. 3. However, the statistical significance does not represent clinical significance because some variables could influence the P-value, such as sample size. For this study, we observed that low SLC25A11 expression was associated with poor prognosis in the ICGC and GSE54236 cohorts, but the P-value did not indicate significance, perhaps because of the sample size. We need to expand the sample size to confirm the prognostic value of SLC25A11 expression levels in the future. Furthermore, we postulate that SLC25A11 plays an essential role in transporting NADH and GSH from the cytoplasm into mitochondria, providing energy for liver cancer cells to withstand harsh environments. However, clinical trials and further experiments are needed to certify these results and clarify the specific molecular mechanism.

Materials and Methods

Data collection and mining. Clinical information and RNA-sequencing expression results were collected from the TCGA dataset, GEO dataset (<https://www.ncbi.nlm.nih.gov/gds/>), HCCDB dataset (<http://lifeome.net/database/hccdb/>) and ICGC dataset (<https://icgc.org/>). All these data were processed in R software (version 3.6.1) (<https://www.r-project.org/>) and related packages³¹.

Statistical analysis. Box plots were used to evaluate the expression of SLC25A11 in the TCGA-Liver Hepatocellular Carcinoma (LIHC) dataset. A receiver operating characteristic curve (ROC) was drawn to assess the diagnostic significance of SLC25A11 expression by using the pROC package³². In accordance with the threshold identified by the ROC curve, liver cancer patients were separated into low and high expression groups. OS and RFS were compared between low and high groups via Kaplan-Meier analysis with the package in R^{33,34}. Fisher's exact and chi-square tests were utilized to evaluate correlations between the expression of SLC25A11 mRNA and clinical information. The potential prognostic factors were selected by Cox analysis. Correlations between SLC25A11 expression and survival and other clinical characteristics of patients were confirmed by using multi-factor Cox analysis. * $p < 0.05$ was considered significant.

Data availability

All data generated or analyzed during this study are included in this published article.

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Author contributions

Guoqiang Pan collected and analyzed the data. Shengnan Jia made the figures. Ruobing Wang and Yanqing Li made the tables. Yan Jiao wrote the manuscript. Nan Liu designed the study. All authors revised the manuscript and approved the final version to be published.

Competing interests

The authors declare no competing interests.

Additional information

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