Prognostic Values of Stabilin-2 in Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is the primary malignancy of the liver. However, biomarkers for early HCC diagnosis are not available. Stabilin (STAB) proteins are scavenger receptors involved in apoptosis and clearance of hyaluronic acid. The role of STAB in HCC has not been previously explored; therefore, the aim of this study was to assess whether STAB gene expression can be used as a novel HCC biomarker.

Materials and Methods: Data on 370 HCC patients in the Cancer Genome Atlas database and 221 patients in the Gene Expression Comprehensive Database were retrieved and analyzed. Kaplan–Meier analysis and Cox regression model were used to calculate median survival time using hazard ratio (HR) and 95% confidence interval (CI).

Results: The Gene Expression Omnibus dataset showed that high Stabilin-2 (STAB2) expression implies longer overall survival (HR after correction = 0.541; 95% CI, 0.339–0.865; $p = 0.0182$, after correction $p = 0.010$) and longer recurrence-free survival time (adjusted HR = 0.554; 95% CI, 0.376–0.816; $p = 0.0085$, adjusted $p = 0.003$).

Conclusions: STAB2 is a potential biomarker for the diagnosis and prognosis of HCC.

Background

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor worldwide, and the third leading cause of cancer-related deaths accounting for 8.2% of all cancer deaths. China contributes to about half of the new liver cancer cases and deaths recorded worldwide every year [1, 2]. Hepatocellular carcinoma accounts for about 90% of liver tumors and causes more than 700,000 deaths worldwide each year due to poor prognosis [3, 4]. Cirrhosis is a main hepatocellular carcinoma risk factor and about 70–90% of hepatocellular carcinoma patients have a cirrhosis history [5]. Chronic hepatitis B virus (HBV) infection is one of the high risk factors for human HCC, accounting for 50% to 80% of the HCC cases worldwide [6]. In addition, alcoholism, aflatoxin B1 intake, non-alcoholic fatty liver and hepatitis C virus are also risk factors for hepatocellular carcinoma [7–9]. Although surgical resection and liver transplantation can effectively treat HCC, the 5-year overall survival rate remains at 7% [10]. Early screening for liver cancer relies on liver ultrasound and alpha-fetoprotein (AFP) [11]. However, ultrasound monitoring is limited by low detection sensitivity, which often leads to misdiagnosis of malignant nodules [12]. AFP is also reported to have low sensitivity and specificity [13]. Recent studies have reported potential HCC diagnostic markers such as protein induced by vitamin K absence or antagonist-II (PIVKA-II), Lens culinaris-agglutinin-reactive fraction of AFP (AFP-L3), MicroRNA-4651 (miR-4651) and MicroRNA-125b (miR-125b) [14–17]. HCC diagnosis using these markers requires invasive procedures, therefore, there is need to identify non-invasive biomarkers.

Stabilin-1 (STAB1) and Stabilin-2 (STAB2) also known as FEEL-1 and FEEL-2, are structurally highly conserved type I transmembrane proteins and members of the scavenger receptor family [18]. Previous

studies report that STAB is implicated in the proliferation and distant metastasis of melanoma cells, lymph node metastasis of prostate cancer and tongue cancer[19-21]. However, few studies have explored STAB expression in HCC. Therefore, our study utilized multiple datasets to explore the relationship between STAB expression levels and HCC.

Materials And Methods

Patient information

We retrieved STAB1 and STAB2 mRNA expression levels data for HCC patients from The Cancer Genome Atlas (TCGA) database. We normalized and transformed the raw data using R software (RStudio 1.2.5001 Inc., Boston, MA, USA). The expression levels were classified into high and low groups using a 50% cutoff value. Processed data for 370 patients including race, gender, age, TNM stage, body mass index (BMI), family history, survival status and time were also retrieved.

Further, the GSE14520 dataset consisting of [HT_HG-U133A] Affymetrix HT human genome U133A array (445 samples) and [HT_HG-U133A_2] Affymetrix HT human genome U133A genes was downloaded from the Gene Expression Synthesis (GEO) database. The expression data consisted of a 2.0 array (57 samples) [22, 23]. To avoid batch effects, we obtained mRNA expression data from 221 HCC patients selected from the TCGA dataset. The mRNA expression levels in 221 HCC patients were also divided into two groups using a 50% cutoff value.

GraphPad Prism version 7.0 (GraphPad Software, La Jolla, CA, USA) for Windows was used to assess differential gene expression between primary liver tumors and normal liver tissues. Mutations in the STAB gene family were verified using cBioPortal webserver for Cancer Genomics.

Survival analysis

We evaluated the prognosis of HCC patients from the TCGA database using median survival time (MST) and we adjusted for race, gender, age, BMI, TNM staging, and family history using the Cox regression model. We assessed the prognosis of HCC patients in the GEO database using the overall survival (OS) and recurrence-free survival (RFS). Further, we adjusted for gender, age, hepatitis B virus (HBV) infection status, alanine aminotransferase (ALT) status, main tumor size, multinodule status, cirrhosis, alphafetoprotein (AFP) level, and Barcelona Clinic Liver Cancer (BCLC) stage using the Cox proportional hazards regression model in the GEO database.

Stratified chi-square test

We stratified the data and calculated the MST, hazard ratio (HR) at 95% confidence interval (CI). These data revealed differences in the different layers.

Functional enrichment analysis

We performed a gene ontology (GO) functional analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis using Metascape (a gene annotation and analysis tool) and the Database for Annotation, Visualization, and Integrated Discovery (DAVID) version 6.8[24-26]. In GO analysis, we assessed biological processes, cellular components, and molecular functions. Further, we used the STRING (Search Interaction Gene / Protein Search Tool) database to predict protein-protein interactions between STAB gene family members and other proteins [27].

Statistical Analysis

We used GraphPad Prism version 7.0 for Windows to generate survival curves and forest plots. All other statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Result

Gene expression in tumors and normal tissues

Presentation of STAB1 and STAB2 expression data from the TCGA dataset on a scatter plot showed that these two factors have different expressions levels (Fig. 1a, b). However, STAB1 and STAB2 were not differentially expressed (Fig. 1c, d) in tumor tissues and normal tissues of the GEO dataset. In addition, 7% of cancer samples showed STAB1 mutations, including missense mutation, truncating mutation, amplification, and deep deletion. Further, 5% of cancer samples showed mutations in the STAB2 gene including missense mutation, truncating mutation, amplification (Fig. 1e).

Basic patient information

Detailed information on the 370 HCC patients in TCGA database is shown in Table 1. BMI and TNM staging showed a significant correlation with MST ($p = 0.021$ and <0.001 , respectively). Information on patients evaluated in the GEO database is shown in Table 2. Major tumor size, TNM stage, cirrhosis, BCLC stage, and alpha-fetoprotein levels were significantly correlated with OS ($p = 0.003, 0.019, <0.001, <0.001, <0.001, 0.032, 0.019, \text{ and } 0.026$, respectively). Further, Gender, TNM stage, and BCLC stage were significantly correlated with RFS ($p = 0.016, <0.001, \text{ and } <0.001$, respectively).

Table 1 Basic characteristics of HCC patients in the TCGA database

Variables	Patients (n=370)	No. of events (%)	MST [months]	HR (95%CI)	Log-rank <i>P</i>
Race					0.127
Asian	157	44(28.0%)	82	Ref	
White+others	203	81(40.1%)	68	1.42(0.98-2.05)	
Missing	10				
Gender					0.488
Male	249	79(31.7%)	57	Ref	
Female	121	51(42.1%)	59	1.07(0.89-1.28)	
Age					0.248
≤60	177	55(31.1%)	71	Ref	
>60	193	75(38.9%)	52	1.23(0.87-1.75)	
BMI					0.021
≤25	177	61(34.5%)	68	Ref	
>25	157	51(32.5%)	66	0.82(0.64-1.04)	
Missing	36				
TNM staging					<0.001
I+II	274	76(27.7%)	84	Ref	
III+IV	94	54(57.4%)	26	2.40(1.69-3.41)	
Missing	2				
Family history					0.192
Yes	112	49(44.1%)	40	Ref	
No	207	69(33.3%)	62	0.78(0.54-1.13)	
Missing	51				

MST, median survival time; HR, hazard ratio; 95%CI, 95% confidence interval; Ref, reference; BMI, body mass index; TNM stage, tumor, node and metastasis stage.

Survival analysis

The TCGA data were analyzed using a multivariate Cox regression model with adjustment for race, gender, age, BMI, TNM stage, and family history, which showed no significant correlation between STAB1 and STAB2 with prognosis (adjusted $p=0.300$ and 0.865 respectively) (Fig. 2a, b, g). GEO data were evaluated by a multiple Cox regression model, with adjustment for race, age, HBV, ALT, major tumor size, multiple nodule status, liver cirrhosis, TNM staging, BCLC staging, and AFP, showing that STAB2 was significantly correlated with OS (HR = 0.541; 95% CI, 0.339–0.865; adjusted $p = 0.010$) and RFS (HR = 0.554; 95% CI, 0.376-0.816; adjusted $p = 0.003$) after adjustment (Fig. 2c, d, e, f, h, i).

Stratified chi-square test

We performed a hierarchical chi-square test on all clinical features. The results showed that high expression of STAB2 implied a more favorable prognosis in male, HBV (CC + NO), ALT > 50u / L, non-multinodular, cirrhosis, early TNM(I and II), early BCLC (0 and A) and AFP ≤ 300ng/ml ($p=0.013, 0.008, 0.039, 0.040, 0.024, 0.018, 0.010$ and 0.038 respectively). (Table 3)

Functional enrichment analysis

GO analysis showed STAB2 gene assembly in Hyaluronan catabolic process, hyaluronan metabolic process, regulation of calcineurin–NFAT signaling cascade, aminoglycan catabolic process, glycosaminoglycan catabolic process, mucopolysaccharide metabolic process, aminoglycan metabolic process, glycosaminoglycan metabolic process, carbohydrate derivative catabolic process, glycosaminoglycan binding, organonitrogen compound catabolic process cellular response to fibroblast growth factor stimulus, regulation of cell–substrate adhesion, regulation of apoptotic signaling pathway and cell migration. KEGG pathway enrichment showed that members of the STAB gene family is implicated in glycosaminoglycan degradation–vitamin digestion and absorption–fat digestion and absorption, ECM–receptor interaction–shigellosis–bile secretion–gastric acid secretion–cardiac muscle contraction, hematopoietic cell lineage–salivary secretion–pancreatic secretion–proteoglycans in cancer–thyroid hormone signaling pathway–adrenergic signaling in cardiomyocytes–cAMP signaling pathway–Epstein–Barr virus infection–and regulation of actin cytoskeleton. Details of the enrichment analysis are shown in Fig. 3b and Fig. 3b.

Analysis of the protein-protein interaction network using the STRING database shows that STAB1 and STAB2 are directly or intermediately related to some hub genes in HCC (such as CD44 and APOB) (Fig. 4).

Table 2. Basic characteristics of HCC patients in the GEO database

Variables	Patients (n=221)	MST	OS HR(95%CI)	Log-rank P	MST	RFS HR(95%CI)	Log-rank P
Gender				0.149			0.016
Female	30	55	Ref		51	Ref	
Male	191	48	1.70(0.82-3.52)		38	2.17(1.13-4.14)	
Age							
≤60	181	49	Ref	0.903	46	Ref	0.985
>60	40	48	0.97(0.55-1.69)		37	1.00(0.63-1.60)	
HBV status				0.449			0.411
AVR-CC	56	45	Ref		29	Ref	
CC+NO	162	50	0.91(0.12-6.74)		48	1.22(0.61-2.44)	
Missing	3						
ALT				0.726			0.229
≤50u/L	130	49	Ref		53	Ref	
>50u/L	91	49	1.08(0.70-1.66)		40	1.25(0.87-1.78)	
Main tumor size				0.003			0.100
≤5cm	140	53	Ref		51	Ref	
>5cm	81	41	1.88(1.22-2.89)		30	1.36(0.94-1.97)	
Multinodular				0.055			0.427
Yes	45	37	Ref		37	Ref	
No	176	47	0.63(0.39-1.01)		41	0.84(0.54-1.30)	
Cirrhosis				0.019			0.056
Yes	203	48	Ref		39	Ref	
No	18	64	0.22(0.05-0.88)		54	0.46(0.20-1.04)	
TNM staging				<0.001			<0.001
I+II	169	54	Ref		53	Ref	
III	49	30	0.65(0.33-1.30)		18	0.79(0.19-3.19)	
Missing	3						
BCLC staging				<0.001			<0.001
0+A	168	54	Ref		45	Ref	
B+C	51	30	0.52(0.26-1.05)		33	0.69(0.35-1.35)	
Missing	2						
AFP				0.032			0.229
≤300ng/ml	118	53	Ref		49	Ref	
>300ng/ml	100	44	1.63(1.06-2.50)		31	1.24(0.87-1.78)	
Missing	3						

OS, overall survival; RFS, recurrence-free survival; HBV status , hepatitis B virus status ; AVR-CC, active viral replication chronic carrier; CC, chronic carrier; ALT, alanine aminotransferase; AFP, alpha fetoprotein; TNM stage, tumor, node and metastasis stage ; BCLC staging, Barcelona Clinic Liver Cancer.

Table 3. Stratified chi-square test of basic characteristics of HCC patients in the GEO database

Variables	Patients (n=221)	No. of events (%)	MST [months]	OS HR(95%CI)	Log-rank P
Gender					
Female					0.734
low expression	13	3[23.1%]	56	Ref	
high expression	17	5[29.4%]	54	1.28[0.31-5.37]	
Male					0.013
low expression	97	48[49.5%]	44	Ref	
high expression	94	29[30.9%]	52	0.56[0.35-0.89]	
HBV status					
AVR-CC					0.865
low expression	31	14[45.2%]	46	Ref	
high expression	25	11[44.0%]	45	1.07[0.49-2.36]	
CC+NO					0.008
low expression	76	36[47.4%]	45	Ref	
high expression	86	23[26.7%]	55	0.50[0.29-0.84]	
Missing	3				
ALT					
≤50u/L					0.191
low expression	63	27[42.9%]	46	Ref	
high expression	67	21[31.3%]	51	0.68[0.39-1.21]	
>50u/L					0.039
low expression	47	24[51.1%]	43	Ref	
high expression	44	13[29.5%]	54	0.49[0.25-0.96]	
Multinodular					
Yes					0.413
low expression	26	15[57.7%]	41	Ref	
high expression	19	8[42.1%]	47	0.70[0.30-1.65]	
No					0.04
low expression	84	36[42.9%]	46	Ref	
high expression	92	26[28.3%]	54	0.59[0.36-0.98]	
Cirrhosis					
Yes					0.024
low expression	102	50[49.0%]	44	Ref	
high expression	101	33[32.7%]	51	0.60[0.39-0.94]	
No	18				0.892
low expression		1[12.5%]	56	Ref	
high expression	10	1[10.0%]	63	0.83[0.05-13.21]	
TNM staging					
I+II					0.018
low expression	83	33[39.8%]	50	Ref	
high expression	86	20[23.3%]	58	0.51[0.29-0.89]	
III					0.422
low expression	24	17[70.8%]	28	Ref	
high expression	25	14[56.0%]	32	0.75[0.37-1.52]	
Missing	3				
BCLC staging					
0+A					0.01
low expression	83	33[39.8%]	50	Ref	
high expression	85	18[21.2%]	58	0.47[0.26-0.83]	
B+C					0.756

low expression	25	17 (68.0%)	28	Ref	
high expression	26	16 (61.5%)	31	0.90	0.45-1.78
Missing	2				
AFP					
≤300ng/ml					0.038
low expression	49	22 (44.9%)	49	Ref	
high expression	69	17 (24.6%)	56	0.51	0.27-0.96
>300ng/ml					0.378
low expression	59	29 (49.2%)	41	Ref	
high expression	41	17 (41.5%)	47	0.76	0.42-1.39
Missing	3				

OS, overall survival; RFS, recurrence-free survival; HBV status, hepatitis B virus status; AVR-CC, active viral replication chronic carrier; CC, chronic carrier; ALT, alanine aminotransferase; AFP, alpha fetoprotein; TNM stage, tumor, node and metastasis stage; BCLC staging, Barcelona Clinic Liver Cancer.

Discussion

In this study, we investigated the association between Stabilin family genes and HCC. The findings show that the changes in mRNA expression level of Stabilin-2 are effective in HCC prognosis. Stabilin-1 is expressed in non-continuous sinusoidal endothelium of liver, spleen, adrenal cortex, lymph node and sinusoidal macrophages[21]. Stabilin-1 is a multifunctional transmembrane protein involved in scavenging, cell adhesion, lymphocyte transmigration and angiogenesis[28]. A previous study reports that high levels of Stabilin-1 peritumoral macrophages are positively correlated with survival ($p=0.04$) in colorectal cancer. However, in more advanced stages (Stage IV), patients with a high number of peritumoral or intratumoral Stabilin-1 macrophages showed a shorter disease-specific survival ($p=0.05$, and $p=0.008$, respectively) [28]. In addition, previous studies have reported that Stabilin-1 is associated with the prognosis of bladder urothelial carcinoma and oral squamous cell carcinoma[29, 30]. Riabov V demonstrated that Stabilin-1 is expressed on tumor-associated macrophages (TAM) in human breast cancer, and with higher expression levels recorded in stage I [31]. In addition, higher Stabilin-1 expression levels are observed at inflammatory sites with increased leucocyte recruitment and vessels supplying HCCs [32]. In our study, Stabilin-1 mRNA expression in liver cancer and normal tissues was significantly different, however, Stabilin-1 levels showed no significant correlation with HCC prognosis.

Stabilin-2 is expressed in low levels in several human tissues, but highly expressed in non-continuous sinusoidal endothelium of liver, lymph node, spleen and bone marrow tissues[33]. This protein serves as a hyaluronan receptor in endocytosis, as a scavenger receptor that binds to bacteria, and as a protein that endocytoses modified low-density lipoprotein and the end-products of glycation [19]. A previous study reports that Stabilin-2 can be used as a diagnostic biomarker for detecting prostate cancer in seminal plasma [34]. Further, a systemic block of Stabilin-2 was found to inhibit lymph node (LN) metastasis in an orthotopic prostate cancer model [20]. Therefore, Stabilin-2 may be associated with lymph node metastasis of tumors. Notably, a previous study reported that Stabilin-2 was significantly associated with lymph node metastasis in tongue, lung, stomach, and colon cancer, and was implicated in tongue cancer

prognosis [19]. Stabilin-2 modulates LN metastasis through Stabilin-2-mediated homotypic interaction between tumor cells and LN. Hyaluronic acid (HA) is a biopolymer composed of repeating units of disaccharides, which consisting of D-glucuronic acid and N-acetylglucosamine molecules linked by β -(1–4) and β -(1–3)glycosides[35]. HA has been shown to regulate proliferation, invasion, cell movement, multidrug resistance, and epithelial-mesenchymal transition in many in vivo and in vitro tumor cell lines[36]. Stabilin-2 is a key HA scavenger receptor, which mediates macrophage binding and engulfs bacteria or apoptotic cells [37]. HA levels are used as non-invasive biomarker to assess liver fibrosis [38]. Cirrhosis, the highest stage of liver fibrosis, is the main risk factor for HCC. HCC cells treated with HA show aggressive proliferation, migration and energy metabolism properties in vitro[39]. Preoperative high serum HA levels predict poor prognosis for HCC patients after liver resection [40]. In our study, STAB2 expression level was higher in normal liver tissue compared with liver cancer tissue. High expression of STAB2 implies a better prognosis in HCC tissues. Therefore, we presume that STAB2 may be a protective factor for HCC, which may be related to the clearance of HA. However, another study reported that absence of STAB2 in tissues surrounding tumors is associated with longer survival [41]. Notably, inhibition of Stabilin-2 increases circulating hyaluronic acid levels and prevents tumor metastasis [18]. However, the findings from this study were not consistent with previous findings, therefore, the relationship between STAB2 and HCC should be explored with larger samples and molecular methods.

STAB2 expression was shown to improve the symptoms of patients with certain characteristics such as male, HBV (CC + NO), high level of ALT (ALT > 50u / L), non-multinodular, cirrhosis, early TNM(I and II), early BCLC (0 and A), and AFP $\leq$ 300ng / ml. ($p=0.012, 0.007, 0.035, 0.038, 0.022, 0.016, 0.008$ and 0.035 respectively). These effects may have amalgamative effect on STAB2 thus improving the protective role on HCC. Previous studies have shown that low level of AFP, early stages of TNM and BCLC are positively correlated with the HCC prognosis [42, 43].

In GO and KEGG functional enrichment analyses, we found that STAB2 plays a role in the metabolism of mucopolysaccharide metabolic process, glycosaminoglycan metabolic process, glycosaminoglycan binding, fat digestion and absorption, regulation of cell–substrate adhesion and regulation of apoptotic signaling pathway. In a previous study, stichopus japonicus acid mucopolysaccharide (SJAMP) effectively inhibited the growth of HCC through the stimulation of immune organs and tissue proliferation[44]. In addition, inhibitors of glycosaminoglycan biosynthesis may affect liver metastasis potential of tumor cells[45]. The proteoglycan composed of protein core and glycosaminoglycan chain plays a vital role in the development of HCC, and is been explored as a potential HCC biomarker and therapeutic target[46]. Glycosaminoglycans are involved in HA synthesis, and Stabilin-2 as the main scavenger receptor for systemic HA[47], is involved in regulating HA metabolic pathways as reported previously. Reduction of CD44 may lead to reduced cell-substrate adhesion of fibroblasts, resulting in cell migration and invasion[48]. Non-alcoholic steatohepatitis (NASH) is a common cause of cirrhosis and hepatocellular carcinoma (HCC). Studies have shown that a high-fat diet promotes serum cholesterol levels in mice liver, subsequently increases vascular endothelial-derived growth factor (VEGF) levels, and ultimately leads to high proliferation of liver tumor cells[49]. STAB2 acts as a scavenger receptor and is implicated in cell apoptosis [50]. Defective or inadequate apoptosis may increase metastasis, tumor

progression, and tumor cell radiotherapy[51]. Apoptosis also plays an important role in the development of liver cancer.

Based on the protein-protein interaction results, STABs interacts with some hub genes in HCC, including CD44 and APOB. A recent study showed that the initiation of HCC requires the inhibition of p53 by CD44-enhanced growth factor signaling[52]. In another study, APOB inactivation was shown to be associated with poor outcome in patients with HCC, therefore, APOB may play a role in regulating multiple genes involved in HCC development [53].

However, our research has limitations. First, our sample size is small. Second, we studied single genes, therefore they should be analyzed in conjunction with other genes. Finally, more clinical data should be collected to evaluate the relationship between STAB gene family and HCC. This clinical information may include smoking, drinking, Child-Pugh score, arterial chemoembolization, antitumor status, number of tumors, tumor envelope status, intrahepatic metastasis and vascular invasion.

Conclusion

In conclusion, Our research reports that the expression levels of STAB2 are higher in HCC tissue than in normal tissue and STAB2 is significantly correlated with OS and RFS. It may be a potential HCC prognostic marker.

Abbreviations

HCC : Hepatocellular carcinoma ; STAB: Stabilin; HR: hazard ratio; CI: confidence interval; HBV: hepatitis B virus; AFP: alpha-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; miR: microRNA; TCGA: The Cancer Genome Atlas; GEO: Gene Expression Synthesis; MST: median survival time; OS: overall survival; RFS : recurrence-free survival; ALT: alanine aminotransferase; BCLC: Barcelona Clinic Liver Cancer; GO: gene ontology; TAM: tumor-associated macrophages; LN: lymph node; HA: hyaluronic acid; SJAMP: stichopus japonicus acid mucopolysaccharide; NASH: non-alcoholic steatohepatitis; DAVID: Database for Annotation, Visualization, and Integrated Discovery; KEGG: Kyoto Encyclopedia of Genes and Genomes; AVR–CC, active viral replication chronic carrier; CC, chronic carrier; TNM, tumor, node and metastasis; BMI: body mass index; VEGF: vascular endothelial-derived growth factor .

Declarations

Acknowledgment

Not applicable

Authors' contributions

ZD and WZ designed the study; ZD and PZ analyzed the data; ZD wrote the manuscript; LY, KC, JY and WZ revised the manuscript. All authors read and approved the final .

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Availability of data and materials

The datasets generated and analyzed during the current study are available in the TCGA and GEO repository.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

STAB1 and STAB2 gene expression levels between tumor and normal tissue in the TCGA (A, B). STAB1 and STAB2 gene expression levels between tumor and normal tissue in the GEO dataset (C, D). Genetic alteration information of the STAB gene family (E). ***: $p < 0.001$, ****: $p < 0.0001$, ns: no significant difference.

Figure 2

Kaplan–Meier overall survival curves and forest plots of the STAB gene family in TCGA (A, B, G). Overall survival curves and forest plots of the STAB gene family (C, D, H), as well as recurrence-free survival and forest plots (E, F, I) in the GEO dataset.

Figure 3

GO (A) and KEGG (B) enrichment analysis of the two STAB genes.

Figure 4

Protein-protein interaction networks among the Stabilin-1, Stabilin-2 and other proteins.