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S100 family members: potential therapeutic target in patients with hepatocellular carcinoma

A STROBE study

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Abstract

Proteins in S100 family exhibit different expressions patterns and perform different cytological functions, playing substantial roles in certain cancers, carcinogenesis, and disease progression. However, the expression and role of S100 family members in the prognosis of hepatocellular carcinoma (HCC) remains unclear. To investigate the effect of S100 family members for the prognosis of liver cancer, we assessed overall survival (OS) using a Kaplan–Meier plotter (KM plotter) in liver cancer patients with different situation. Our results showed that 15 members of the S100 family exhibited high levels of expression and these levels were correlated with OS in liver cancer patients. The higher expression of S100A5, S100A7, S100A7A, S100A12, S100Z, and S100G was reflected with better survival in liver cancer patients. However, worse prognosis was related to higher levels of expression of S100A2, S100A6, S100A8, S100A9, S100A10, S100A11, S10013, S100A14, and S100P. We then evaluated the prognostic values of S100 family members expression for evaluating different stages of AJCC-T, vascular invasion, alcohol consumption, and the presence of hepatitis virus in liver cancer patients. Lastly, we studied the prognostic values of S100 family members expression for patients after sorafenib treatment. In conclusion, our findings show that the proteins of S100 family members exhibit differential expression and may be useful as targets for liver cancer, facilitating novel diagnostic and therapeutic strategies in cancer.

Abbreviations: CIs = 95% confidence intervals, EDC = epidermal differentiation complex, EOC = epithelial ovarian cancer, ERK1/2 = extracellular signal-regulated kinase 1/2, ESCC = esophageal squamous-cell carcinoma, GEO = Gene Expression Omnibus, HCC = hepatocellular carcinoma, HRs = Hazard ratios, KM plotter = Kaplan–Meier plotter, MAPK = mitogen-activated protein kinase, NF-κB = Nuclear factor-kappa-B, NSCLC = non-small-cell lung cancer, OPSCC = oropharyngeal squamous cell carcinoma, OS = overall survival, OSCC = oral squamous-cell carcinoma, RAGE = advanced glycation end-product, TNF-γ = Tumor necrosis factor-γ.

Keywords: Kaplan–Meier survival plots, liver cancer, S100 family, survival

1. Introduction

Hepatocellular carcinoma (HCC) is the most commonly diagnosed primary liver cancer, and its incidence continues to increase.[1–3] Hepatocellular carcinoma is the fifth-most aggressive malignant tumor worldwide and is the second-largest cancer-related mortality worldwide,[4] causing more than 700,000 deaths every year.[5] Due to the rapid progress of liver cancer and fewer effective drugs in patients. Therefore, exploring new therapeutic targets in the prognosis of liver cancer has aroused great interest.

The S100 protein family consisting of small acidic Ca^{2+} combined with cytotoxic proteins composed of cells and tissues

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was first isolated from bovine brain tissue by Moore et al in 1965. The family consists of at least 20 known human members.[6] The term S100 was named on the basis of the solubility of these proteins in 100% ammonium sulfate.[7] The S100 family has the following five genetically encoded loci: S100P is located on 4p16; S100Z is located on 21q22; S100G is located on Xp22; and the remaining members are located on chromosome 1q21, in a gene cluster called the epidermal differentiation complex (EDC).[8] Most genes of the human S100 family members proteins are clustered at the chromosomal region on 1q21, a region that undergoes frequent rearrangements in cancers. As a consequence, S100 family members proteins may be implicated in tumorigenesis and tumor progression.[9–11] Each individual S100 family member has a highly consistent sequence and structure, but cannot be replaced functionally.[12] S100 family members play various roles in regulating cell proliferation, differentiation, apoptosis, migration, and invasion through interactions with a variety of target proteins, such as Nuclear factor-kappa-B (NF-κB), p53, and β-catenins.[8–9,13] In addition, S100 family members may contribute to the development of many types of malignant tumors, autoimmune diseases, and chronic inflammatory diseases.[14]

At present, large amounts of evidence have suggested that dysregulation of S100 family members proteins is related to several types of tumors, such as renal carcinoma, ovarian cancer, and colorectal cancer.[9,15,16] S100 family members exhibit a distinctive level of protein expression among diverse malignant tumors, different tumor subtypes, and clinicopathological grades. However, S100 family members play different roles in certain tumors. For example, S100A2 acts as an unfavorable prognostic marker for non-small cell lung cancer (NSCLC)[17,18] and pancreatic cancer.[7] However, it also serves as a favorable prognostic predictor for oral cell carcinoma (OSCC)[19] and esophageal squamous-cell carcinoma (ESCC).[9,20] Most S100 family members, such as S100A4, S100A6, S100A8, and S100A9, have been reported to be involved in liver cancer. Extracellular S100A9 enhances the activation of the mitogen-activated protein kinase (MAPK) signaling system via combination with the receptor advanced glycation end-product (RAGE).[21] Advanced glycation end-product (RAGE) plays a significant role in some inflammation-related cancers and facilitates carcinogenesis and tumor progression via stimulation of advanced glycation end-product (RAGE). RAGE-dependent mitogen-activated protein kinase (MAPK) and Nuclear factor-kappa-B (NF-κB) signaling pathways.[22,23] A variety of S100 family members proteins, including S100A4, S100A6, S100A7, S100A8, S100A9, S100A8/9, S100A12, S100B, and S100P are ligands for advanced glycation end-product (RAGE).[24] Additionally, S100A9 has been shown to be upregulated in HepG2 HCC cells via activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (MAPK) signal-transduction pathways, which subsequently contribute to the proliferation, invasion, and development of liver cancer cells.[25–27] Liang et al have also suggested that the expression of S100A9 was higher in HCC.[26–28] Furthermore, Arai et al have demonstrated that S100A9 upregulation is correlated with poorly differentiated liver carcinomas.[29] In contrast, other investigators have found that S100A9 protects Hep3B HCC cells from Tumor necrosis factor-γ (TNF-γ)-induced apoptosis via upregulation of *S100A9* gene expression in the HCC cells of humans and mice.[22]

However, some additional S100 family members, such as 100A1, S100A3, A100A5, and S100G, have rarely been reported in liver carcinoma. Therefore, we investigated that the expression and prognostic value of additional S100 family members in live cancer.

2. Materials and methods

Online database developed with gene expression data and survival information of liver cancer subjects downloaded from the Gene Expression Omnibus (GEO) (GSE9843, GSE20017, GSE9843) were used to analyze the relationship between the mRNA expression of individual S100 family members and the overall survival (OS) in liver cancer patients.[30] Clinical data, the stage of AJCC-T, vascular invasion, alcohol consumption, hepatitis virus exposure, and sorafenib treatment, were included in the database. Briefly, by respectively setting different clinical parameters, the survival plots of 20 individual S100 family proteins was obtained by importing S100 family proteins into the Kaplan–Meier plotter (KM plotter) database (https://kmplot.com/analysis/index.php?p=service&cancer=liver_rnaseq), which contains updated gene expression data and survival information are from 364 liver cancer patients. The requested mRNA RNA-seq expression below or above median allowed us to classify the cases into low expression group and high expression group Subsequently, Kaplan–Meier survival plots, hazard ratios (HRs), 95% confidence intervals (CIs), and log ranks were obtained from the webpage. $P < .05$ was established as being statistical difference. P-value $< .01$ was set as statistically significant to reduce the false-positive rate.

3. Results

3.1. The differential expression of S100 family member in liver cancer patients

We first detected the expression of every individuals S100 family member in liver cancer patients. Survival curves of all of the patients are shown in Figure 1. Among them, we discovered that the mRNA expression of S100A5 (HR = 0.37, 95% CI: 0.26–0.53, $P = 6.1e{-}09$), S100A7 (HR = 0.48, 95% CI: 0.34–0.68, $P = 2.6e{-}05$), S100A7A (HR = 0.37, 95% CI: 0.26–0.52, $P = 4.5e{-}09$), S100G (HR = 0.36, 95% CI: 0.25–0.51, $P = 1.7e{-}09$), S100Z (HR = 0.59, 95% CI: 0.41–0.86, $P = .0049$), and S100A12 (HR = 0.64, 95% CI: 0.44–0.91, $P = .014$) were higher in liver cancer, which indicated with better survival. However, the high expression of S100P (HR = 1.63, 95% CI: 1.16–2.31, $P = .0049$), S100A2 (HR = 1.74, 95% CI: 1.22–2.49, $P = .0021$), S100A6 (HR = 1.69, 95% CI: 1.16–2.44, $P = .0051$), S100A9 (HR = 2.00, 95% CI: 1.39–2.88, $P = 1.3e{-}04$), S100A10 (HR = 1.79, 95% CI: 1.25–2.56, $P = .0012$), S10011 (HR = 1.85, 95% CI: 1.31–2.62, $P = 4.0e{-}04$), S10013 (HR = 1.45, 95% CI: 1.03–2.05, $P = .034$), S10014 (HR = 1.58, 95% CI: 1.01–2.46, $P = .042$), and S100A8 (HR = 1.48, 95% CI: 1.03–2.13, $P = .032$) were correlated with a worse survival in liver cancer. Among these negative expression P values, S100A2, S100A6, S100A9, S100A10, S10011, and S100P were considered to be great statistically significant. There was no connection between patient survival and the remainder of the S100 family members.

3.2. The differential expression of S100 family members correlates with survival in liver cancer patients with different clinicopathological characteristics

We further analyzed the effect of S100 family members on prognosis of liver cancer in different clinicopathological

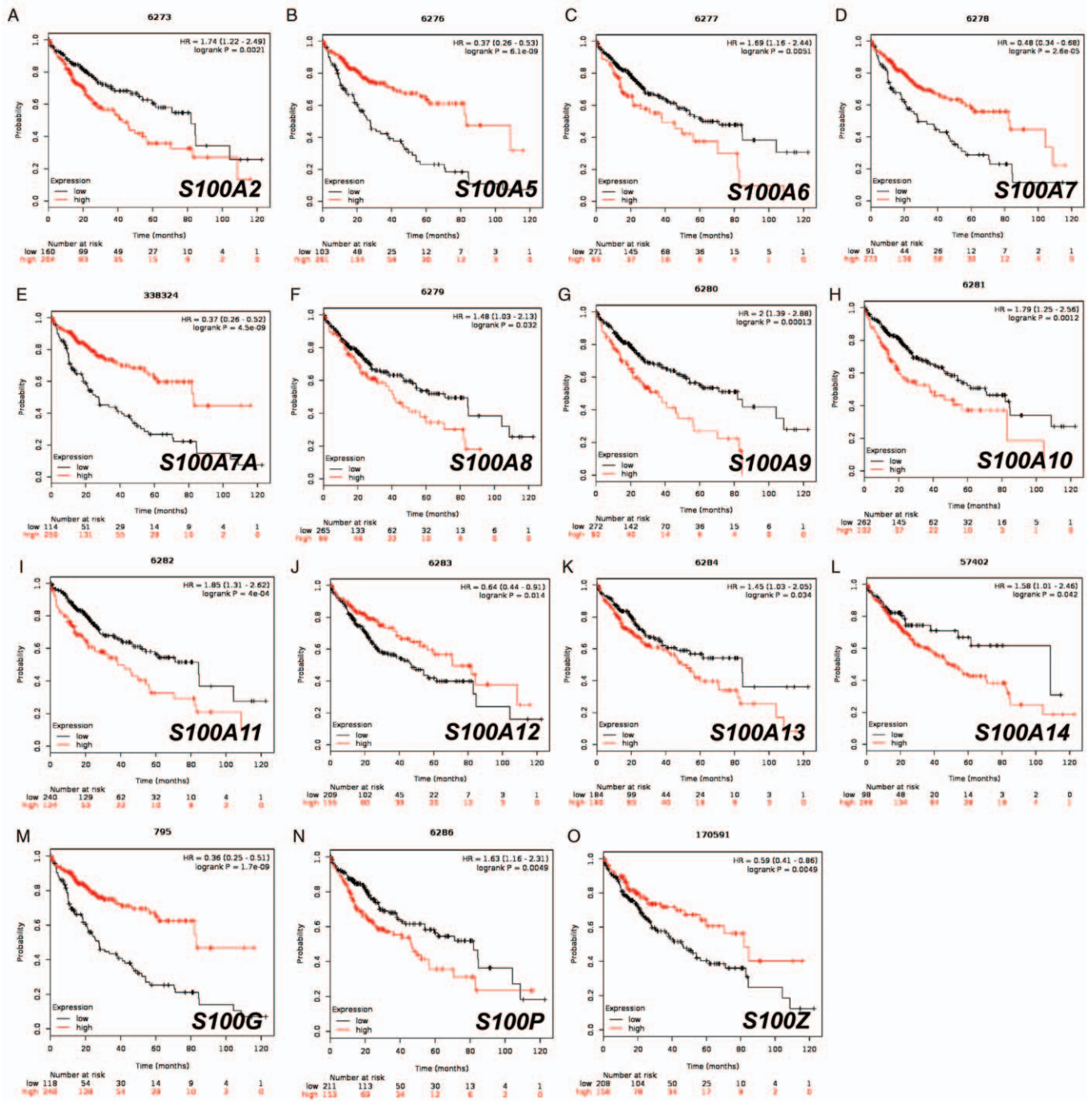

Figure 1. The differential expression of S100 family member in liver cancer patients. (A) S100A2 (RNA-seq ID: 6273), (B) S100A5 (RNA-seq ID: 6276), (C) S100A6 (RNA-seq ID:6277), (D) S100A7 (RNA-seq ID: 6278), (E) S100A7A (RNA-seq ID: 338324), (F) S100A8 (RNA-seq ID: 6279), (G) S100A9 (RNA-seq ID: 6280), (H) S100A10 (RNA-seq ID: 6281), (I) S100A11 (RNA-seq ID: 6282), (J) S100A12 (RNA-seq ID: 6283), (K) S100A13 (RNA-seq ID: 6284), (L) S100A14 (RNA-seq ID: 57402), (M) S100G (RNA-seq ID: 795), (N) S100P (RNA-seq ID: 6286), (O) S100Z (RNA-seq ID: 170591) are plotted for all of the patients (n = 364).

characteristics, including AJCC-T staging (Figs. 2–4 and Table 1), vascular-invasion status (Table 2). As shown in Figure 2 and Table 1, we found that a favorable OS in AJCC-T-type-1 liver cancer patients is associated with higher mRNA expression of S100A5 (HR = 0.4, 95% CI: 0.22–0.73, $P = .0018$), S100A1 (HR = 0.46, 95%CI: 0.25–0.85, $P = .011$), and S100G (HR = 0.46, 95% CI: 0.25–0.84, $P = .0096$). In contrast, higher mRNA expression of S100P (HR = 1.89, 95% CI: 1.05–3.38, $P = .03$), S100A9 (HR = 1.95, 95% CI: 1.09–3.5, $P = .022$), S100A16 (HR = 1.95, 95% CI: 1.08–3.53, $P = .024$), S100A2 (HR = 1.97, 95% CI: 1.08–3.60, $P = .025$), S100A11 (HR = 2.06, 95% CI: 1.14–3.71, $P = .014$), S100A7 (HR = 2.11, 95% CI: 1.13–3.96, $P = .017$), S100A7A (HR = 2.18, 95% CI: 1.14–4.19, $P = .017$), and S100A10 (HR = 2.28, 95% CI: 1.17–4.45, $P = .013$) were related to a worse OS in AJCC-T-type-1 liver cancer patients, among these negative expression P values, there was no P values

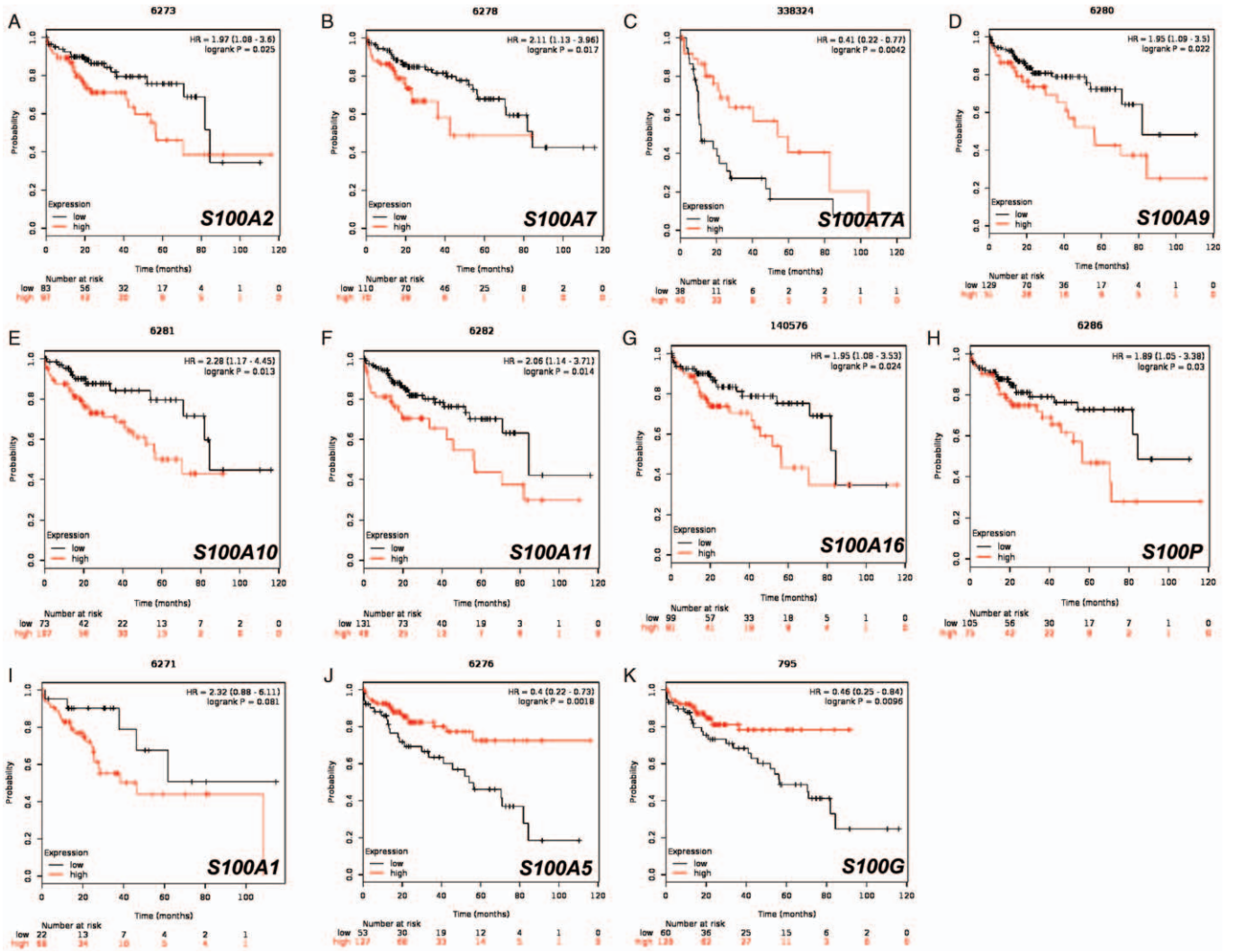

Figure 2. The differential expression of S100 members correlates with liver cancer patients in AJCC-T-type-1. (A) S100A2 (RNA-seq ID: 6273), (B) S100A7 (RNA-seq ID: 6278), (C) S100A7A (RNA-seq ID:338324), (D) S100A9 (RNA-seq ID: 6280), (E) S100A10 (RNA-seq ID: 6281), (F) S100A11 (RNA-seq ID: 6282), (G) S100A16 (RNA-seq ID: 140576), (H) S100P (RNA-seq ID: 6286), (I) S100A1 (RNA-seq ID: 6271), (J) S100A5 (RNA-seq ID: 6276), (K) S100G (RNA-seq ID: 795) are plotted for all of the patients (n = 180).

considered to be great statistically significant. For AJCC-T-type-2 liver cancer patients, as shown in Figure 3 and Table 1, S100A7A (HR = 0.2sssa8, 95% CI: 0.12–0.65, $P = .0017$), S100G (HR = 0.31, 95% CI: 0.15–0.66, $P = .0012$), S100A5 (HR = 0.33, 95% CI: 0.16–0.69, $P = .0022$), and S100A12 (HR = 0.44, 95% CI: 0.21–0.95, $P = .032$) were correlated with longer OS times. In contrast, the expression of S100A10 (HR = 2.32, 95% CI: 1.2–4.84, $P = .02$), S100A13 (HR = 2.32, 95%CI: 1.08–5.01, $P = .026$), S100A9 (HR = 2.52, 95%CI: 1.19–5.34, $P = .013$), S100A14 (HR = 3.44, 95% CI: 1.03–11.49, $P = .033$), and S100A16 (HR = 4.05, 95% CI: 1.22–13.41, $P = .013$) were correlated with shorter OS times, among these negative expression P values, there was no P values considered to be great statistically significant. In AJTT-C-type-3 patients, as shown in Figure 4 and Table 1, the expression levels of S100Z (HR = 0.4, 95% CI: 0.21–0.77, $P = .0049$), S100A7 (HR = 0.45, 95% CI: 0.24–0.82, $P = .0079$), S100A7A (HR = 0.41, 95% CI: 0.22–0.77, $P = .0042$), and S100G (HR = 0.43, 95% CI: 0.23–0.82, $P = .0081$) were correlated with longer OS time. In contrast, the expression levels of S100P (HR = 1.92, 95%CI:1.03–3.57, $P = .036$), S100A4 (HR = 1.99, 95% CI: 1.02–3.89, $P = .04$), S100A11 (HR = 2.06, 95% CI: 1.11–3.83, $P = .02$), S100A13 (HR = 2.1, 95% CI: 1.08–4.11, $P = .026$), S100A2 (HR = 2.2, 95% CI: 1.17–4.14, $P = .013$), and S100A10 (HR = 2.45, 95% CI: 1.33–4.52, $P = .0032$) were correlated with shorter OS times, among these negative expression P values, there was only S100A10 considered to be great statistically significant.

Subsequently, we investigated the relationship between S100 proteins and vascular invasion status. Because we found few cases of macrovascular invasion patients, we compared microvascular invasion status with none-vascular-invasion status in liver cancer patients. We found S100A5 (HR = 0.26, 95% CI: 0.12–0.58, $P = .00033$), S100G (HR = 0.37, 95% CI: 0.17–0.79, $P = .0077$), S100A7A (HR = 0.38, 95% CI: 0.18–0.82, $P = .01$), and S100A12 (HR = 0.42, 95% CI: 0.19–0.92, $P = .025$) were better prognosis in microvascular invasion liver cancer patients (Table 2). In contrast, S100A9 (HR = 2.61, 95% CI: 1.14–5.99, $P = .018$), S100P (HR = 2.85, 95% CI: 1.2–6.75, $P = .013$),

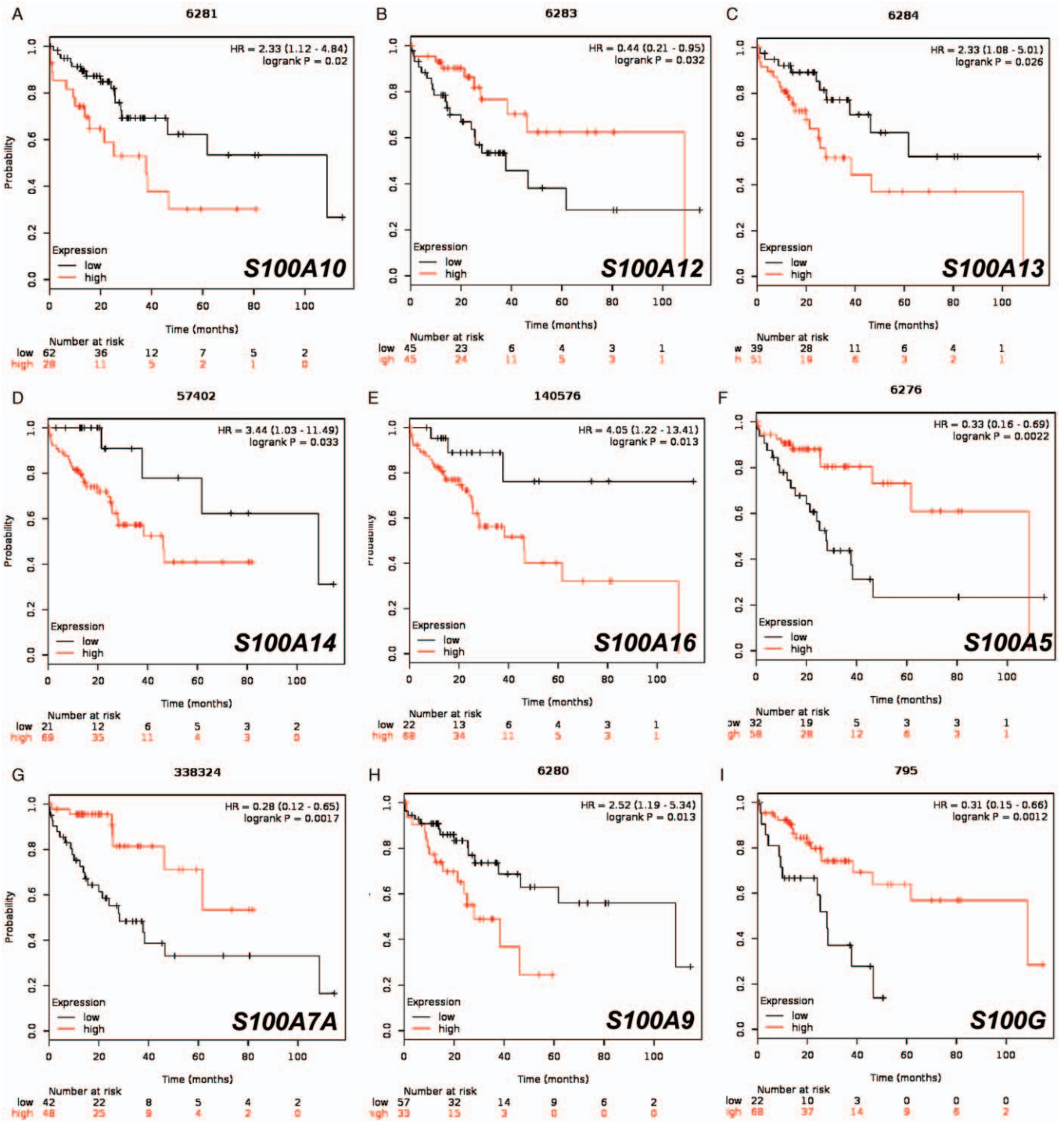

Figure 3. The differential expression of S100 members correlates with liver cancer patients in AJCC-T-type-2. (A) S100A10 (RNA-seq ID: 6281), (B) S100A13 (RNA-seq ID: 6284), (C) S100A9 (RNA-seq ID:6280), (D) S100A14 (RNA-seq ID: 57402), (E) S100A16 (RNA-seq ID: 140576), (F) S100A7A (RNA-seq ID: 33824), (G) S100G (RNA-seq ID: 795), (H) S100A5 (RNA-seq ID: 6276), (I) S100A12 (RNA-seq ID: 6283) are plotted for all of the patients (n = 90).

S100A7 (HR = 2.88, 95% CI: 1.34–6.19, $P = .0046$), S100A14 (HR = 3.63, 95% CI: 1.09–12.11, $P = .025$), and S100A11 (HR = 4.95, 95% CI: 1.16–21.07, $P = .017$) predicted worse prognosis in microvascular invasion liver cancer subjects (Table 2), among these negative expression P values, there was only S100A7 considered to be statistically significant. In none-vascular-invasion patients, S100G (HR = 0.31, 95% CI: 0.18–0.51, $P =$ 2.0e−06), S100A5 (HR = 0.32, 95% CI: 0.19–0.53, $P =$ 3.6e−06), S100A7A (HR = 0.33, 95% CI: 0.2–0.55, $P =$ 8.8e−06), S100A7 (HR = 0.38, 95% CI: 0.23–0.63, $P = .00013$), S100A1 (HR = 0.39, 95% CI: 0.21–0.74, $P = .0029$), S100Z (HR = 0.44, 95% CI: 0.25–0.76, $P = .0023$), S100A12 (HR = 0.54, 95% CI: 0.31–0.93, $P = .023$), and S100A8 (HR = 0.57, 95% CI: 0.34–0.96, $P = .031$) exhibited better prognosis

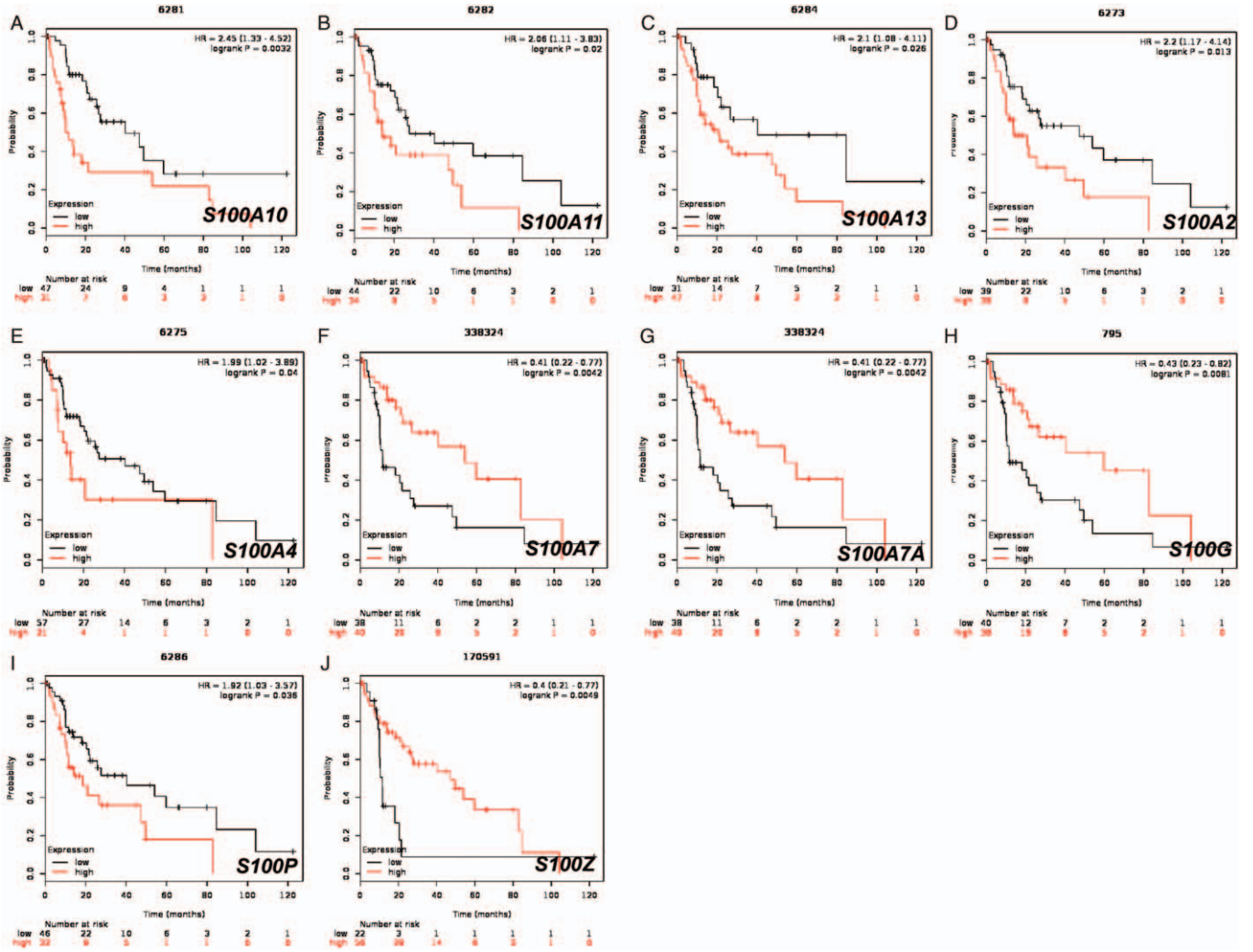

Figure 4. The differential expression of S100 members correlates with liver cancer patients in AJCC-T-type-3. (A) S100A2 (RNA-seq ID: 6273), (B) S100A4 (RNA-seq ID: 6275), (C) S100A10 (RNA-seq ID: 6281), (D) S100A11 (RNA-seq ID: 6282), (E) S100A13 (RNA-seq ID: 6284), (F) S100P (RNA-seq ID: 6286), (G) S100A7 (RNA-seq ID:6287), (H) S100A7A (RNA-seq ID: 338324), (I) S100G (RNA-seq ID: 795), (J) S100Z (RNA-seq ID: 170591) are plotted for all of the patients (n = 78).

Table 1

Correlation of S100 gene expression level with overall survival in liver cancer patients with different pathological AJCC-T.

S100 family	RNA-seq ID	AJCC-T	Cases	HR	95% CI	*P*
S100A1	6271	I	180	0.46	0.25–0.85	**.011**
		II	–	–	–	–
		III	78	1.62	0.81–3.24	.17
		IV	13	–	–	–
S100A2	6273	I	180	1.97	1.08–3.60	**.025**
		II	90	1.72	0.73–4.05	.21
		III	78	2.2	1.17–4.14	**.013**
		IV	–	–	–	–
S100A3	6274	I	180	1.5	0.83–2.70	.17
		II	90	0.5	0.24–1.07	.068
		III	78	0.57	0.3–1.08	.079
		IV	–	–	–	–
S100A4	6275	I	180	0.75	0.42–1.35	.34
		II	90	1.58	0.76–3.3	.22
		III	78	1.99	1.02–3.89	**.04**
		IV	–	–	–	–
S100A5	6276	I	180	0.4	0.22–0.73	**.0018**
		II	90	0.33	0.16–0.69	**.0022**

(*continued*)

Table 1

(continued).

S100 family	RNA-seq ID	AJCC-T	Cases	HR	95% CI	*P*
		III	78	0.56	0.3–1.03	.057
		IV	–	–	–	–
S100A6	6277	I	180	1.8	0.99–3.26	.55
		II	90	1.55	0.75–3.23	.24
		III	78	1.68	0.87–3.23	.12
		IV	–	–	–	–
S100A7	6278	I	180	2.11	1.13–3.96	**.017**
		II	90	2.02	0.92–4.43	.073
		III	78	0.45	0.24–0.82	**.0079**
		IV	–	–	–	–
S100A7A	338,324	I	180	2.18	1.14–4.19	**.017**
		II	90	0.28	0.12–0.65	**.0017**
		III	78	0.41	0.22–0.77	**.0042**
		IV	–	–	–	–
S100A8	6279	I	180	0.65	0.36–1.18	.15
		II	90	1.66	0.76–3.62	.2
		III	78	1.63	0.87–3.05	.12
		IV	–	–	–	–
S100A9	6280	I	180	1.95	1.09–3.5	**.022**
		II	90	2.52	1.19–5.34	**.013**
		III	78	1.77	0.92–3.39	.082
		IV	–	–	–	–
S100A10	6281	I	180	2.28	1.17–4.45	**.013**
		II	90	2.33	1.12–4.84	**.02**
		III	78	2.45	1.33–4.52	**.0032**
		IV	–	–	–	–
S100A11	6282	I	180	2.06	1.14–3.71	**.014**
		II	90	2.54	0.96–6.75	.054
		III	78	2.06	1.11–3.83	**.02**
		IV	–	–	–	–
S100A12	6283	I	180	0.61	0.34–1.12	.11
		II	90	0.44	0.21–0.95	**.032**
		III	78	1.41	0.71–2.78	.32
		IV	–	–	–	–
S100A13	6284	I	180	1.23	0.69–2.19	.49
		II	90	2.33	1.08–5.01	**.026**
		III	78	2.10	1.08–4.11	**.026**
		IV	–	–	–	–
S100A14	57,402	I	180	1.35	0.74–2.49	.33
		II	90	3.44	1.03–11.49	**.033**
		III	78	1.76	0.93–3.35	.081
		IV	–	–	–	–
S100A16	140,576	I	180	1.95	1.08–3.53	**.024**
		II	90	4.05	1.22–13.41	**.013**
		III	78	1.32	0.72–2.42	.36
		IV	–	–	–	–
S100B	6285	I	180	1.71	0.82–3.55	.15
		II	90	0.37	0.13–1.08	.058
		III	78	1.37	0.71–2.63	.35
		IV	–	–	–	–
S100G	795	I	180	0.46	0.25–0.84	**.0096**
		II	90	0.31	0.15–0.66	**.0012**
		III	78	0.43	0.23–0.82	**.0081**
		IV	–	–	–	–
S100P	6286	I	180	1.89	1.05–3.38	**.03**
		II	90	1.69	0.77–3.71	.18
		III	78	1.92	1.03–3.57	**.036**
		IV	–	–	–	–
S100Z	170,591	I	180	0.63	0.35–1.14	.12
		II	90	0.52	0.2–1.36	.18
		III	78	0.4	0.21–0.77	**.0049**
		IV	–	–	–	–

The bold values indicate that the results are statistically significant.

Table 2

The differential expression and effect of S100 members in liver cancer patients with vascular invasion status.

S100 family	RNA-seq ID	Vascular invasion	Cases	HR	95% CI	*P*
S100A1	6271	none	203	0.39	0.21–0.74	**.0029**
		Micro	90	2.37	0.82–6.87	.1
		Macro	–	–	–	–
S100A2	6273	none	203	1.39	0.83–2.33	.21
		Micro	90	2.52	0.94–6.75	.058
		Macro	–	–	–	–
S100A3	6274	none	203	1.44	0.83–2.52	.2
		Micro	90	2.85	0.85–9.5	.075
		Macro	–	–	–	–
S100A4	6275	none	203	0.73	0.43–1.24	.24
		Micro	90	2.43	0.91–6.46	.066
		Macro	–	–	–	–
S100A5	6276	none	203	0.32	0.19–0.53	**3.6e–06**
		Micro	90	0.26	0.12–0.58	**3.3e–04**
		Macro	–	–	–	–
S100A6	6277	none	203	0.7	0.41–1.19	.18
		Micro	90	2.22	0.89–5.55	.079
		Macro	–	–	–	–
S100A7	6278	none	203	0.38	0.23–0.63	**1.3e–04**
		Micro	90	2.88	1.34–6.19	**.0046**
		Macro	–	–	–	–
S100A7A	338,324	none	203	0.33	0.2–0.55	**8.8e–06**
		Micro	90	0.38	0.18–0.82	**.01**
		Macro	–	–	–	–
S100A8	6279	none	203	0.57	0.34–0.96	**.031**
		Micro	90	2.07	0.96–4.46	.058
		Macro	–	–	–	–
S100A9	6280	none	203	1.37	0.79–2.37	.25
		Micro	90	2.61	1.14–5.99	**.018**
		Macro	–	–	–	–
S100A10	6281	none	203	1.55	0.9–2.66	.11
		Micro	90	1.99	0.89–4.43	.087
		Macro	–	–	–	–
S100A11	6282	none	203	2.1	1.25–3.51	**.004**
		Micro	90	4.95	1.16–21.07	**.017**
		Macro	–	–	–	–
S100A12	6283	none	203	0.54	0.31–0.93	**.023**
		Micro	90	0.42	0.19–0.92	**.025**
		Macro	–	–	–	–
S100A13	6284	none	203	1.34	0.8–2.24	.27
		Micro	90	1.86	0.84–4.1	.12
		Macro	–	–	–	–
S100A14	57,402	none	203	1.37	0.81–2.32	.24
		Micro	90	3.63	1.09–12.11	**.025**
		Macro	–	–	–	–
S100A16	140,576	none	203	1.42	0.83–2.41	.2
		Micro	90	2.6	0.89–7.61	.071
		Macro	–	–	–	–
S100B	6285	none	203	1.25	0.72–2.18	.42
		Micro	90	3.75	0.88–15.89	.054
		Macro	–	–	–	–
S100G	795	none	203	0.31	0.18–0.51	**2e–06**
		Micro	90	0.37	0.17–0.79	**.0077**
		Macro	–	–	–	–
S100P	6286	none	203	1.56	0.93–2.6	.088
		Micro	90	2.85	1.2–6.75	**.013**
		Macro	–	–	–	–
S100Z	170,591	none	203	0.44	0.25–0.76	**.0023**
		Micro	90	0.72	0.33–1.56	.4
		Macro	–	–	–	–

The bold values indicate that the results are statistically significant.

Table 3

The differential expression and effect of S100 members in liver cancer patients with alcohol consumptions.

S100 family	RNA-seq ID	Alcohol consumption	Cases	HR	95% CI	*P*
S100A1	6271	Yes	115	2.59	1.06–6.32	**.031**
		No	202	0.67	0.42–1.07	.09
S100A2	6273	Yes	115	3.67	1.58–8.53	**.0013**
		No	202	1.68	1.05–2.68	**.029**
S100A3	6274	Yes	115	0.63	0.31–1.25	.18
		No	202	0.7	0.44–1.12	.14
S100A4	6275	Yes	115	1.37	0.72–2.62	.34
		No	202	0.69	0.42–1.12	.13
S100A5	6276	Yes	115	0.42	0.22–0.81	**.0077**
		No	202	0.36	0.23–0.57	**5.8e−06**
S100A6	6277	Yes	115	1.82	0.95–3.51	.069
		No	202	2.18	1.36–3.5	**9.6e−04**
S100A7	6278	Yes	115	2.32	1.18–4.56	**.012**
		No	202	0.47	0.3–0.76	**.0014**
S100A7A	338324	Yes	115	0.36	0.19–0.7	**.0016**
		No	202	0.36	0.23–0.57	**5.6e−06**
S100A8	6279	Yes	115	0.76	0.4–1.43	.39
		No	202	1.87	1.16–3.01	**.0091**
S100A9	6280	Yes	115	1.89	1–3.57	**.047**
		No	202	1.78	1.12–2.81	**.013**
S100A10	6281	Yes	115	1.84	0.97–3.5	.057
		No	202	2.28	1.42–3.66	**4.8e−04**
S100A11	6282	Yes	115	2.32	1.22–4.42	**.0083**
		No	202	1.89	1.19–2.99	**.0058**
S100A12	6283	Yes	115	0.57	0.3–1.08	.08
		No	202	0.74	0.46–1.71	.2
S100A13	6284	Yes	115	2.6	1.31–5.19	**.0048**
		No	202	1.53	0.96–2.44	.073
S100A14	57402	Yes	115	2	1.05–3.79	**.031**
		No	202	0.63	0.37–1.07	.087
S100A16	140576	Yes	115	2.04	1.05–3.97	**.033**
		No	202	1.87	1.03–3.42	**.038**
S100B	6285	Yes	115	0.47	0.23–0.97	**.036**
		No	202	1.35	0.81–2.26	.25
S100G	795	Yes	115	0.3	0.14–0.65	**.0011**
		No	202	0.33	0.21–0.51	**4.7e–07**
S100P	6286	Yes	115	2.61	1.36–5.02	**.0029**
		No	202	1.65	1.04–2.61	**.031**
S100Z	170591	Yes	115	0.41	0.22–0.77	**.0041**
		No	202	0.54	0.33–0.9	**.015**

The bold values indicate that the results are statistically significant.

(Table 2). In contrast, the S100A11 (HR = 2.1, 95% CI: 1.25–3.51, *P* = .004) expression predicted unfavorable prognosis in none-vascular-invasion liver cancer patients (Table 2).

3.3. The differential expression of S100 family members correlates with survival in liver cancer patients with various risk factors

We next investigated the relationships between survival and the S100 family members in different risk factors. As shown in Tables 3 and 4. A better OS was exhibited with high expression of S100G (HR = 0.3, 95% CI: 0.14–0.65, *P* = .0011), S100A7A (HR = 0.36, 95% CI: 0.19–0.7, *P* = .0016), S100Z (HR = 0.41, 95% CI: 0.22–0.77, *P* = .0041), S100A5 (HR = 0.42, 95% CI: 0.22–0.81, *P* = .0077) in risk factors of alcohol consumption. In contrast, S100A11 (HR = 2.32, 95% CI: 1.22–4.42, *P* = .0083), S100A13 (HR = 2.6, 95%CI: 1.31–5.19, *P* = .0048), S100P (HR = 2.61, 95% CI: 1.36–5.02, *P* = .0029), and S100A2 (HR = 3.67, 95% CI: 1.58–8.53, *P* = .0013) predicted a worse prognosis, they are all considered to be great statistically significant. High expression of S100G (HR = 0.31, 95% CI: 0.16–0.59, *P* = .00019), S100A5 (HR = 0.35, 95% CI: 0.18–0.66, *P* = .00082), S100A7A (HR = 0.38, 95% CI: 0.2–0.73, *P* = .0025), and S100A14 (HR = 0.43, 95% CI: 0.18–1.02, *P* = .0048) were better OS for patients with hepatitis virus compared with absent hepatitis virus. In contrast, S100A10 (HR = 2.32, 95% CI: 1.2–4.48, *P* = .0099), S100A2 (HR = 2.48, 95% CI: 1.25–4.9, *P* = .0071), S100P (HR = 2.48, 95% CI: 1.29–4.76, *P* = .0049), and S100A6 (HR = 2.64, 95% CI: 1.36–5.15, *P* = .003) expression predicted a worse prognosis, they are all considered to be statistically significant.

3.4. The differential expression of S100 family members correlates with survival in liver cancer patients with Sorafenib treatment

We finally researched the prognostic significance of each individuals S100 family member in liver cancer patients with

Table 4

The differential expression and effect of S100 members in liver cancer patients with hepatitis virus exposure.

S100 family	RNA-seq ID	Hepatitis virus	Cases	HR	95% CI	*P*
S100A1	6271	Yes	150	2.09	0.87–5.05	.093
		No	167	1.43	0.86–2.39	.17
S100A2	6273	Yes	150	2.48	1.25–4.9	**.0071**
		No	167	1.91	1.09–3.32	**.021**
S100A3	6274	Yes	150	1.7	0.87–3.31	.12
		No	167	0.52	0.32–0.84	**.0065**
S100A4	6275	Yes	150	0.6	0.31–1.18	.13
		No	167	0.84	0.54–1.32	.44
S100A5	6276	Yes	150	0.35	0.18–0.66	**8.2e–04**
		No	167	0.41	0.26–0.66	**1.1e–04**
S100A6	6277	Yes	150	2.64	1.36–5.15	**.003**
		No	167	0.78	0.49–1.24	.3
S100A7	6278	Yes	150	2.09	1.08–4.06	**.026**
		No	167	0.52	0.33–0.83	**.0049**
S100A7A	338,324	Yes	150	0.38	0.2–0.73	**.0025**
		No	167	0.39	0.24–0.63	**7.1e–05**
S100A8	6279	Yes	150	1.54	0.78–3.03	.21
		No	167	0.72	0.45–1.13	.15
S100A9	6280	Yes	150	2.13	1.11–4.08	**.02**
		No	167	1.62	0.99–2.63	.05
S100A10	6281	Yes	150	2.32	1.2–4.48	**.0099**
		No	167	2.22	1.41–3.49	**4e–04**
S100A11	6282	Yes	150	2.26	1.17–4.37	**.012**
		No	167	0.74	0.45–1.23	.25
S100A12	6283	Yes	150	1.78	0.78–4.06	.17
		No	167	0.56	0.36–0.89	**.013**
S100A13	6284	Yes	150	1.66	0.78–3.53	.18
		No	167	1.81	1.14–2.86	**.01**
S100A14	57,402	Yes	150	0.43	0.18–1.02	**.0048**
		No	167	1.54	0.95–2.51	.076
S100A16	140,576	Yes	150	1.84	0.84–4.02	.12
		No	167	1.58	0.96–2.6	.073
S100B	6285	Yes	150	2.01	0.88–4.58	.09
		No	167	0.62	0.36–1.09	.093
S100G	795	Yes	150	0.31	0.16–0.59	**1.9e–04**
		No	167	0.39	0.24–0.63	**6.7e–05**
S100P	6286	Yes	150	2.48	1.29–4.76	**.0049**
		No	167	1.63	1.04–2.56	**.0033**
S100Z	170,591	Yes	150	0.53	0.26–1.1	.084
		No	167	0.5	0.31–0.82	**.005**

The bold values indicate that the results are statistically significant.

Sorafenib treatment. Survival curves of all of the patients are shown in Figure 5. Among them, we discovered that higher mRNA expression of S100A12 (HR = 0.2, 95% CI: 0.06–0.69, $P = .0048$) was shown with better survival in liver cancer after Sorafenib treatment. High expression of S100A8 (HR = 6.56, 95% CI: 1.67–25.79, $P = .0021$), S100A16 (HR = 4.55, 95% CI: 1.39–14.86, $P = .006$) were represented worse survival in liver cancer after Sorafenib treatment.

4. Discussion

S100 proteins are often abnormally expressed in human many tumors, but the mechanisms by which individual S100 family members contribute to disease occurrence remain to be further elucidated.[31] The role of S100A1, S100A3, S100A10, S100A11, S100A12, S100A13, and S100A14 in liver cancer and the prognostic role of S100A5, S100A7, S100A7A, S100A15, S100A16, S100P, S100B, and S100G have not been reported before our study. In our study, it was detected that the mRNA expression of six S100 proteins in liver cancer were found to be significantly closely associated with a better outcome, and nine were found to be associated with worse outcomes, and 5 proteins were not associated with survival. We then particularly evaluated the prognostic value of the great statistically significant relevant S100 family members in liver cancer, including S100A4, S100A6, S100A8, S100A9, S100A13, and S100A14. The details are as follows.

S100A4, a crucial part of the S100 family members, maps to the 1q21 human chromosome and is best recognized for its significant part in promoting cancer progression and metastasis. Additionally, S100A4 has a vital part in the invasion, progression, and metastasis of human malignant tumors.[32–34] It has been reported that S100A4 may be used as a prognostic marker for several types of cancers. Additionally, S100A4 has a significant role in metastasis and poor prognosis in a few human malignancies, including breast cancer, non-small-cell lung cancer

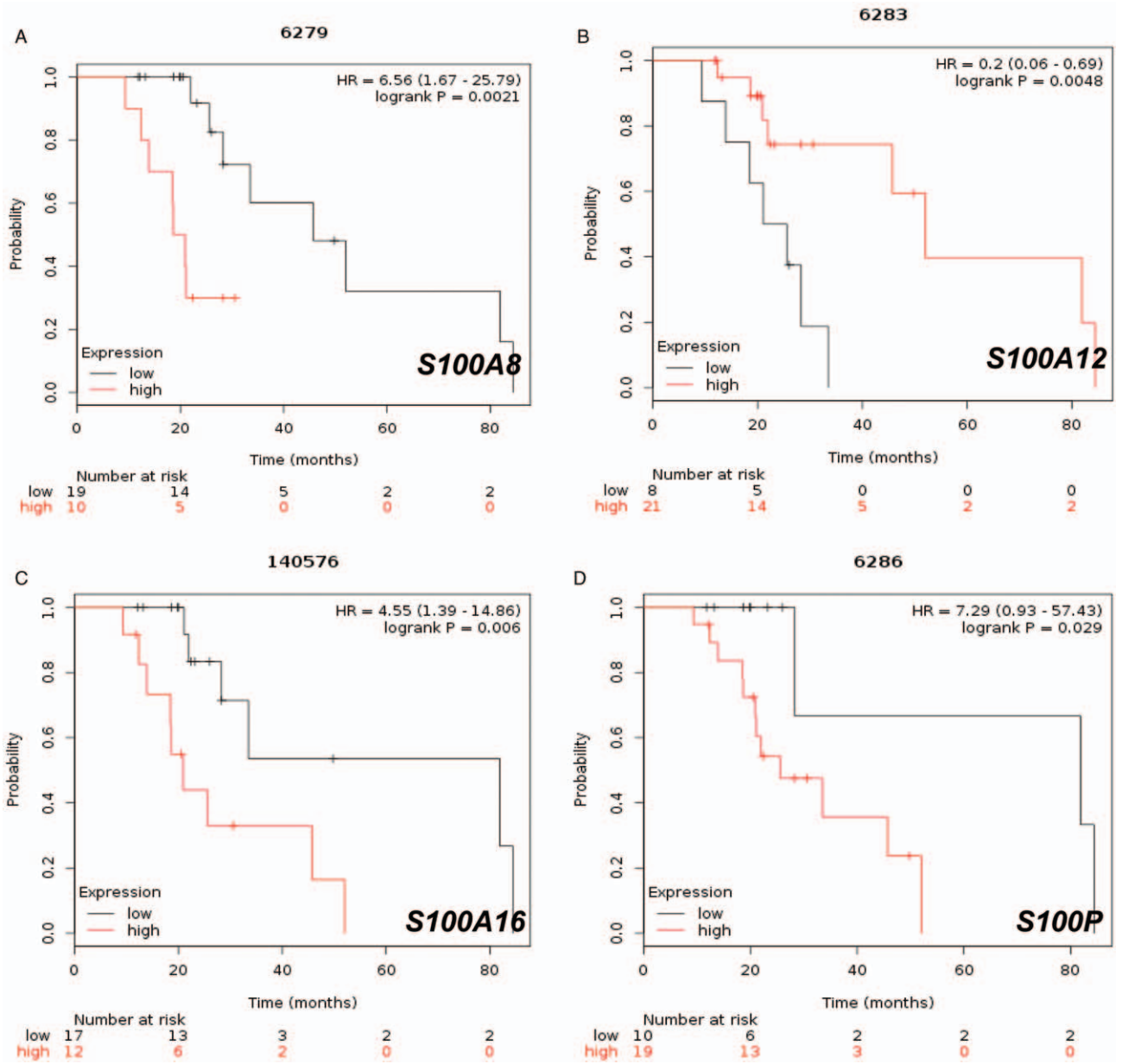

Figure 5. The differential expression of S100 members correlates with liver cancer patients after sorafenib treatment. (A)(S100A8 (RNA-seq ID: 6279), (B) S100A12 (RNA-seq ID: 6283), (C) S100A16 (RNA-seq ID: 140576), (D) S100P (RNA-seq ID: 6286).

(NSCLC), gastric cancer, and chemoresistant ovarian cancer cells.[33,34] In HCC, the abnormal expression of S100A4 correlated with tumor differentiation, invasion, recurrence, aggressive, metastasis, and OS. In addition, many experiments have shown that S100A4 is a tumor marker of HCC, and its increased expression has an adverse effect on the prognosis of HCC.[34–37] However, our data indicated that high mRNA expression of S100A4 was not associated with prognosis of HCC, including the state of vascular invasion, alcohol consumption, AJCC-T type 1, AJCC-T type 2, the presence of hepatitis virus, or sorafenib treatment. Surprisingly, it was found that S100A4 is associated with the poor prognosis of AJCC-T type 3 liver cancer in our study.

S100A6 is a signal transduction intracellular protein located on chromosome 1q21, which is often changed in cancer and plays a role in tumor development. S100A6, which binds to a large number of target proteins, has been shown to regulate a variety of biological functions, such as cell proliferation, cell cycle, Ca^{2+} homeostasis, and apoptosis.[38–40] Emerging evidence has revealed that S100A6 may also be involved in the regulation of tumorigenesis and cancer progression. Furthermore, S100A6 upregulation has been shown to be linked with poor outcome in many malignant tumors, such as gastric cancer, pulmonary adenocarcinoma, colorectal adenocarcinomas, osteosarcoma, lung cancer, HCC, colorectal cancer, cholangiocarcinoma, pancreatic cancer, and intrahepatic cholangiocarcinoma.[38,41–43] In contrast, downregulation of S100A6 correlated with a poor prognosis for prostate and oral cancer.[9] Consequently, S100A6 plays a crucial role in pancreatic, gastric, and prostate cancer, as well as melanoma, non-small-cell lung cancer (NSCLC), and HCC.[44,45] Prior to our study, few reports

have focused on the role of S100A6 in liver cancer. Hua et al confirmed that S100A6 is a marker of poorly differentiated HCC.[46] Consistent with previous studies, Qiang et al report that S100A6 is overexpressed in human liver cancer cells and is involved in promoting the proliferation and migration of human liver cancer.[47] Our study confirmed this finding, and we further found that the increase in S100A6 mRNA expression indicates that the OS of patients with liver cancer, especially hepatitis virus patients, is poor. Besides, our results demonstrated that a high level of S100A6 was not associated with prognosis of AJCC-T, vascular invasion, sorafenib treatment, or hepatitis virus.

S100A8 and S100A9, a heterodimeric EF-hand Ca^{2+} binding intracellular proteins, were originally discovered in cells of the myeloid lineage and were related with inflammatory processes and several types of cancer progression.[9,48–50] Two of S100 family members have a wide span of intracellular and extracellular activities, such as in cell proliferation, apoptosis, cytoskeletal formation and the role of transcriptional factors.[6,51] Many evidence suggest that S100A8 and S100A9 contribute to various inflammation-associated cancer proliferation, progression, invasion, and metastasis.[9,52,53] Multiple studies have shown that under the conditions of inflammatory microenvironment, persistent inflammation stimulation can promote and exacerbate malignancy tumors. Under inflammatory conditions, up-regulation of S100A8/S100A9 has been discovered in various human cancer types,[52,54] such as gastric cancer, colon cancer, breast cancer, liver cancer, lung cancer, prostate cancer, bladder cancer, ovarian cancer, squamous cervical cancer, and skin cancer. However, other studies have revealed a novel role for S100A8/S100A9 acting as a tumor suppressor by promoting cytotoxicity and apoptosis.[22,54] Contrary to these studies, S100A8/S100A9 has been shown to facilitate HCC development by activating mitogen-activated protein kinase (MAPK) signaling pathways.[55] Notably, Wu et al found that S100A8/A9 promotes HepG2 HCC cell proliferation and invasion through activating extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinases (MAPKs).[26] Additionally, a number of epidemiological experiments have indicated that S100A8 and S100A9 might be implicated in HCC development. Up-regulation of S100A8/S100A9 expression in human liver cancer is related to poor differentiation and vascular invasion.[27,29] Our results confirm that increased S100A8/S100A9 mRNA expression is associated with a worse outcome. Furthermore, our outcomes reveal that higher lever S100A9 is correlated with a poor prognosis in liver cancer patients with AJCC-T type 1, AJCC-T type 2, microvascular invasion, the presence of the hepatitis virus, and those that consumed alcohol.

S100A12 is a member of the S100 family members of calcium binding proteins and is expressed in neutrophilic granulocytes. S100A12 is also derived from lymphocytes and monocytes in small amounts.[56,57] There is already some evidence to support that S100A12 promotes growth and vascular invasion, and plays an important role in tumor recurrence and metastasis.[58,59] Funk et al showed that S100A2 protein overexpression is an effective prognostic marker in oropharyngeal squamous cell carcinoma (OPSCC).[29,60] Another study showed that low expression of S100A12 is an unfavorable prognostic factor for survival of gastric carcinoma.[59] Based on previous research, this study reveals the relationship between S100A12 and poor tumor differentiation.[9] In addition, similar to S100A4, S100A12 indicates poor tumor differentiation during HCC progression. Cai et al found that the high expression of S100A12 in the tumor indicates a poor prognosis for patients undergoing HCC surgical resection.[61] Contrary to our expectation, our findings reveal that S100A12 is significantly associated with better OS for patients with liver cancer, especially for those with AJCC-T type 2 and an absence of vascular invasion, alcohol consumption and sorafenib treatment.

S100A14, an EF-hand calcium-binding protein, is initially cloned and characterized in human lung cancer. Previous studies have suggested that the overexpression of S100A14 protein is not only implicated in the dysregulation of cell proliferation /differentiation and metastasis of human tumors, but it also plays a significant role in tumor progression.[62] S100A14 is universally overexpressed in multiple cancers, such as ovarian carcinoma, lung carcinoma, and breast carcinoma. In contrast, S100A14 is under-expressed in kidney cancer, colon cancer, rectal cancer, and esophageal cancer.[63] The high expression of S100A14 is correlated with poor survival in subjects with epithelial ovarian cancer (EOC).[62] A report showed that down-regulated expression of S100A14 predicts poor differentiation and poor prognosis in gastric carcinoma.[64] Zhao et al have implicated that S100A14 takes part in tumor aggressiveness and increased expression of S100A14 has been correlated with a poor clinical outcome in HCC.[65] Our results indicate that high mRNA S100A14 expression is associated to an unfavorable OS in all of the patients, especially in patients with AJCC-T type 2, microvascular invasion, and alcohol consumption. However, we have not found any relationship between S100A14 expression and prognosis in liver cancer of patients with AJCC-T type 1, AJCC-T type 3, lack of vascular invasion, absence of alcohol consumption, or absence of hepatitis virus. From the different results observed in our study, we speculate that the influence of S100 proteins depends on the cell subtype and liver cancer test standards. Therefore, histopathological examination is necessary to determine the expression and role of S100 family members in liver cancer tissues. We will further analyze the function and mechanism of each S100 protein in liver cancer.

5. Conclusions

In summary, the values of S100 proteins in the prognosis of liver cancer under different conditions have been studied, which may provide new targets for cancer diagnosis and treatment.

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Author contributions

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