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Distinct prognostic roles of S100 mRNA expression in gastric cancer

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ABSTRACT

Background: The S100 protein family is implicated in tumor invasion and metastasis, but its prognostic roles in gastric cancer (GC) has not been elucidated.

Materials and methods: In the current study, Kaplan-Meier plotter (KM plotter) database integrated the expression data and survival information of 1065 GC patients were downloaded from the Gene Expression Omnibus (GEO) (GSE22377, GSE14210 and GSE51105) that published by the three major cancer centers (Berlin, Bethesda and Melbourne). Then this database was used to explore the prognostic values of mRNA expression of each individual S100 in GC patients. We further assessed the prognostic value of S100 in different Lauren classifications, clinicopathological features and clinical treatment of gastric cancer.

Results: Expression of 12 members of the S100 family correlated with overall survival (OS) for all GC patients. Increased expression of S100A3, S100A5, S100A7, S100A7A, S100A11, S100A13, S100Z and S100 G were found to be strongly associated with worse survival, while S100A8, S100A9, S100B and S100 P were correlated with better prognosis in all GC patients. Further assessment of prognostic values of S100 in gastric cancer with different clinical features indicated that different S100 members may interact with different signaling pathways and exerted different functions in gastric cancer development.

Conclusions: Although the results should be further testified in clinical studies, our findings offer new insights into the contribution of S100 members to GC progression and might promote development of S100 targeted reagents for treating GC.

1. Introduction

Gastric cancer (GC) is the fourth most common malignancy and the second leading cause of cancer-related mortality worldwide [1]. Due to the lack of obvious clinical symptoms at early stage, most patients are diagnosed mainly in advanced stages and have lost the opportunity for surgical therapy [2]. In recent years, with rapid advances of diagnostic technics and therapeutic tactics, the morbidity and mortality rates of GC have shown a steady downward trend [3]. However, the long-term prognosis remains poor and 5-year overall survival rate is still less than 30% by reason of postoperative recurrence and metastasis [4]. Therefore, identification of potential prognostic markers to monitor and intervene in gastric cancer carcinogenesis is urgent.

The S100 members, belonging to acidic-Ca^{2+} binding cytosolic protein family, are composed of at least 25 distinct members [5–8]. The term S100 alludes to the solubility in 100% saturated ammonium sulfate at neural pH. Although S100 family members show a high degree similarity of sequence and structure, they are not functionally interchangeable and they participate in a broad spectrum of biological processes such as proliferation, migration and/or invasion, inflammation and differentiation [9–11]. There are five genomic loci encoded S100 proteins: S100B on the 21q22 chromosome, S100 P on chromosome 4p16, S100Z on chromosome 5q14 and S100 G on the Xp22 chromosome. The other members are coded in two tandem clusters on the chromosome 1q21 [12,13], a region prone to genomic rearrangements, implying that S100 proteins may be involved in tumor progression. Dysregulated S100 protein expression is a common feature in several human cancers [14–17]. The S100 proteins expression exhibits a distinctive pattern that can be both stage-specific and subtype-specific in tumors. For example, S100A2 acts a tumor-promoter role in lung cancer [18], but as a tumor suppressor in oral cancer [19]. S100A7 exerts differing functions in breast cancer depending on different ER (estrogen receptor) status [20]. S100A3 was relatively overexpressed in poorly differentiated and advanced GC tissues, which was also

Abbreviations: GC, gastric cancer; KM, Kaplan-Meier; OS, overall survival; ER, estrogen receptor; GEO, Gene Expression Omnibus; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; CI, confidence interval

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associated with tumor differentiation and TNM stage of GC [21]. Apart from S100A3, other S100 family members, including S100A6, S100A9, S100A11 and S100 P, have been reported to express in GC [22–26]. Furthermore, the high expressions of S100A6, S100A11 and S100 P were correlated with poor survival in GC patients [22,24–26]. However, S100A9 was associated with better prognosis [23]. Nevertheless, some S100 family members, such as S100A2, S100A5, S100A7, S100A7A, S100A13, S100Z and S100 G, have been rarely studied in GC. The prognostic roles of each individual S100, particularly at the mRNA level in GC are still elusive.

Kaplan-Meier (KM) plotter was generated using gene expression data and survival information downloaded from the Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/geo/). The database encompasses overall survival (OS) data for 882 GC patients [27]. To date, some potential cancer-related genes have been reported using the KM plotter for lung cancer [28], breast cancer [29–31] and ovarian cancer [32] in addition to GC. In this study, we investigated the prognostic role of 20 members of S100 mRNA expression in GC patients using the KM plotter database.

2. Materials and methods

The association of individual S100 family members mRNA expression with OS was analyzed on an online database that was established using gene expression data and survival information of 1065 GC patients downloaded from the Gene Expression Omnibus (GEO) (GSE22377, GSE14210 and GSE51105) that supplied by the three major cancer centers (Berlin, Bethesda and Melbourne) [27]. Presently, ovarian cancer [33], lung cancer [28], breast cancer [34] and gastric cancer [27] databases have been generated. Clinical data including clinical stages, Lauren classification, differentiation grade, HER2 status and clinical treatments were collected. Briefly, 20 individual members of S100 protein family were entered into the database (http://kmplot.com/analysis/index.php?p=service&cancer=gastric) respectively and analyzed with setting different clinical parameters. The requested mRNA expression below or above median classified the cases into low expression group and high expression group. Then, Kaplan-Meier survival plots with hazard ratio (HR), 95% confidence intervals (CI), log rank p and the number-at-risk indicated below were displayed on the webpage. p value < 0.01 was considered statistically significant to reduce the false-positive rate.

3. Results

3.1. Prognostic values of S100 family members in all GC patients

We respectively determined the prognostic values of the mRNA expression of twenty S100 family members in GC patients in www.kmplot.com. Among these 20 S100 members, 12 were significantly correlated with prognosis for all GC patients. The survival curves were shown in Fig. 1A-O, we observed high mRNA expression of S100A8, S100A9, S100B and S100 P were associated with better survival (Fig. 1I-M, HR = 0.69, 95%CI: 0.57-0.82, p = 4.3e-05, HR = 0.65, 95%CI: 0.54-0.77, p = 7.9e-07, HR = 0.66, 95%CI: 0.56-0.78, p = 1.3e-06 and HR = 0.74, 95%CI: 0.61-0.88, p = 0.001 respectively). The other 8 members (S100A3, S100A5, S100A7, S100A7A, S100A11, S100A13, S100Z and S100G) were correlated with worse prognosis (Fig. 1A-H, HR = 1.39, 95%CI: 1.17–1.65, p = 0.00017, HR = 1.74, 95%CI: 1.46–2.06, p = 1.3e-10, HR = 1.71, 95%CI: 1.43–2.05, p = 2.6e-09, HR = 1.55, 95%CI: 1.19–2.03, p = 0.0012, HR = 1.85, 95%CI: 1.56–2.2, p = 9.1e-13, HR = 1.55, 95%CI: 1.27–1.88, p = 9.2e-06, HR = 1.4, 95%CI: 1.1–1.78, p = 0.0067 and HR = 1.36, 95%CI: 1.12–1.64, p = 0.0018 respectively). In addition, the mRNA expression levels of S100A2 (Fig. 1N: HR = 1.2, 95%CI: 1.01–1.42, p = 0.036) and S100A6 (Fig. 1O: HR = 0.82, 95%CI: 0.68-0.98, p = 0.028) were modestly associated with prognosis, while the mRNA expression of the other S100 members were not correlated to OS.

3.2. Prognostic values of S100 family members in GC with different Lauren classifications

Next, the prognostic values of S100 family members were assessed in different Lauren classification of GC, including intestinal type and diffuse type. As shown in Fig. 2, for S100A9 (Fig. 2I: HR = 0.61, 95%CI: 0.45-0.84, p = 0.0021) and S100P (Fig. 2J: HR = 0.5, 95%CI: 0.35-0.72, p = 0.00013), their mRNA expression levels were related to longer OS in intestinal type GC patients. For S100A1 (Fig. 2A: HR = 1.81, 95%CI: 1.21–2.69, p = 0.0032), S100A3 (Fig. 2B: HR = 1.89, 95%CI: 1.38–2.6, p = 6.3e-05), S100A5 (Fig. 2C: HR = 2.89, 95%CI: 1.81–4.63, p = 3.6e-06), S100A7 (Fig. 2D: HR = 1.99, 95%CI: 1.41–2.79, p = 6e-05), S100A7A (Fig. 2E: HR = 1.9, 95%CI: 1.2–2.99, p = 0.005), S100A11 (Fig. 2F: HR = 2.43, 95%CI: 1.77–3.34, p = 1.6e-08), S100A13 (Fig. 2G: HR = 1.79, 95%CI: 1.3–2.46, p = 0.00026) and S100A16 (Fig. 2H: HR = 1.69, 95%CI: 1.18–2.42, p = 0.0041), high mRNA expression of those S100A members were linked with lower OS in intestinal type cancers. S100A6 (Fig. 2K: HR = 0.67, 95%CI: 0.48-0.94, p = 0.021), S100A8 (Fig. 2M: HR = 0.68, 95%CI: 0.49-0.93, p = 0.016) and S100G (Fig. 2N: HR = 1.57, 95%CI: 1.1–2.24, p = 0.012) were moderately associated with survival but without statistical difference. The rest members of S100 were not correlated to prognosis in intestinal type GC.

In diffuse type GC, S100A8 (Fig. 3D: HR = 0.62, 95%CI: 0.44-0.88, p = 0.0068), S100A9 (Fig. 3E: HR = 0.61, 95%CI: 0.43-0.86, p = 0.0044), S100A12 (Fig. 3F: HR = 0.52, 95%CI: 0.37-0.75, p = 0.00028) and S100P (Fig. 3G: HR = 0.57, 95%CI: 0.41-0.8, p = 0.0011) were associated with better prognosis. However, mRNA expression of S100A7 (Fig. 3A: HR = 1.93, 95%CI: 1.29–2.89, p = 0.0011), S100A7A (Fig. 3B: HR = 1.66, 95%CI: 1.15–2.39, p = 0.0063) and S100A11 (Fig. 3C: HR = 2.12, 95%CI: 1.51–2.99, p = 9.7e-06) were correlated to worse OS. The expression of S100A4 (Fig. 3H: HR = 1.49, 95%CI: 1.04–2.13, p = 0.027), S100A5 (Fig. 3I: HR = 1.44, 95%CI: 1.02–2.04, p = 0.036), S100A10 (Fig. 3M: HR = 0.66, 95%CI: 0.47-0.94, p = 0.02), S100A13 (Fig. 3J: HR = 1.53, 95%CI: 1.04–2.23, p = 0.028), S100A14 (Fig. 3N: HR = 0.64, 95%CI: 0.45-0.9, p = 0.011), S100A16 (Fig. 3O: HR = 0.69, 95%CI: 0.49-0.98, p = 0.039) and S100B (Fig. 3K: HR = 1.51, 95%CI: 1.05–2.17, p = 0.025) were modestly associated with OS. We found there was no correlation between survival curves of the rest members of S100 (S100A1, S100A2, S100A3, S100A6, S100Z and S100G) and prognosis in diffuse type GC.

3.3. Prognostic values of S100 family members in GC patients with different clinicopathological features and treatment

Furthermore, we determined the correlation of the prognostic values of S100 members with other clinicopathological features, such as clinical stages, differentiation grades, HER2 (human epidermal growth factor receptor 2) status and clinical treatments. As shown in Fig. 4, high mRNA expression of S100A5 (HR = 2.13, 95%CI: 1.32–3.46, p = 0.0016) and S100A7A (HR = 4.16, 95%CI: 1.34–12.91, p = 0.0077) were associated with worse survival in stage I GC. In stage II GC, the mRNA expression of S100A6 (HR = 0.38, 95%CI: 0.21-0.7, p = 0.0012) and S100P (HR = 0.39, 95%CI: 0.22-0.71, p = 0.0013) were linked to better prognosis, whereas S100A7A (HR = 2.51, 95%CI: 1.29–4.89, p = 0.0049) and S100A11 (HR = 2.54, 95%CI: 1.25–5.18, p = 0.0076) were correlated to worse OS. High mRNA expression of S100A8 (HR = 0.5, 95%CI: 0.38-0.67, p = 1.7e-06), S100A9 (HR = 0.47, 95%CI: 0.35-0.63, p = 2e-07), S100B (HR = 0.64, 95%CI: 0.48-0.86, p = 0.0024) and S100P (HR = 0.56, 95%CI: 0.39-0.79, p = 0.00085) were associated with longer OS in stage III GC. However, S100A1 (HR = 1.58, 95%CI: 1.17–2.15, p = 0.0028), S100A5 (HR = 1.81, 95%CI: 1.3–2.52, p = 0.00037), S100A7A (HR = 1.72, 95%CI:

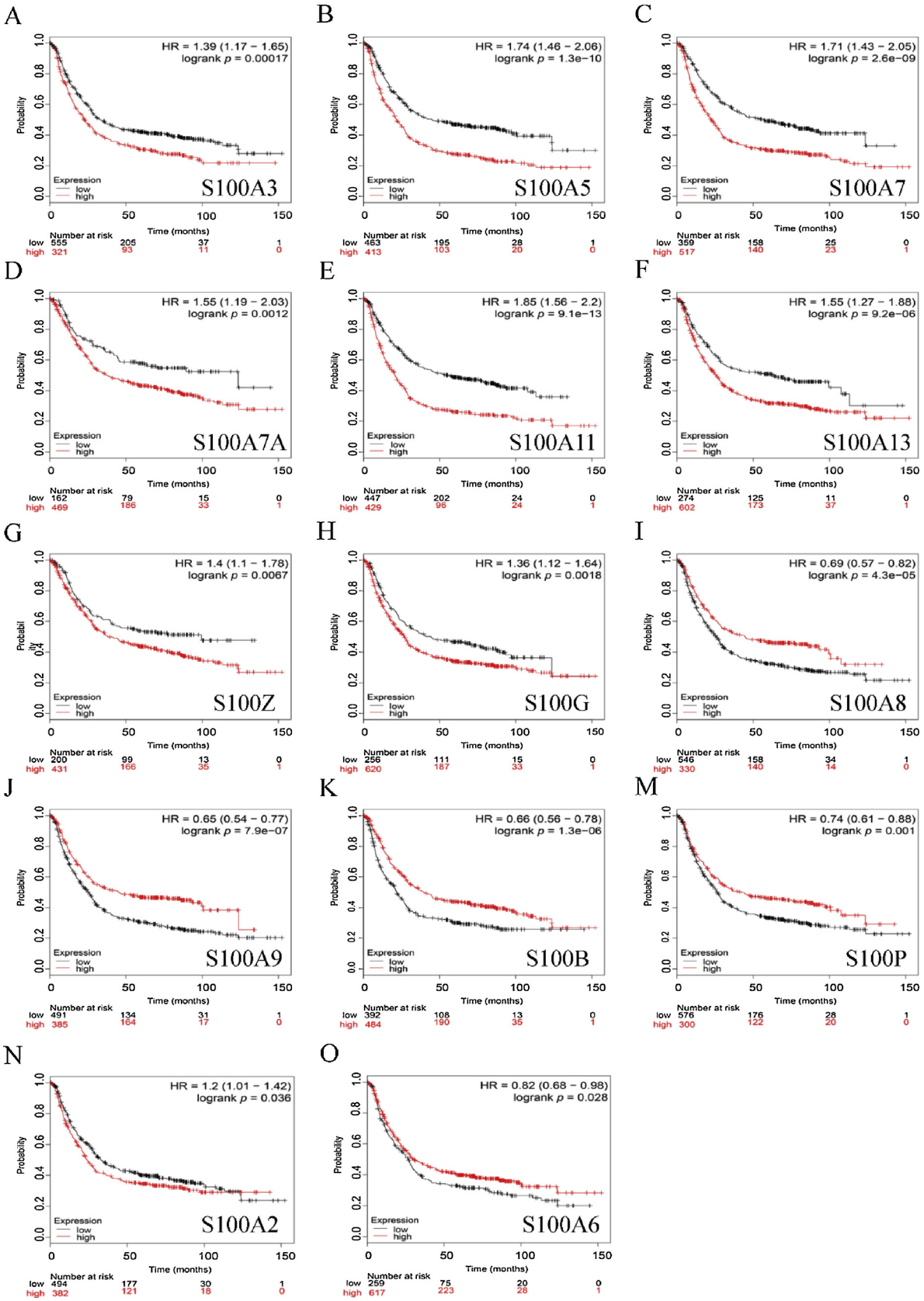

Fig. 1. Survival curves of (A) S100A3 (Affymetrix IDs: 206027_at), (B) S100A5 (Affymetrix IDs: 207763_at), (C) S100A7 (Affymetrix IDs: 205916_at), (D) S100A7A (Affymetrix IDs: 232170_at), (E) S100A11 (Affymetrix IDs: 200660_at), (F) S100A13 (Affymetrix IDs: 202598_at), (G) S100Z (Affymetrix IDs: 1554876_a_at), (H) S100 G (Affymetrix IDs: 207885_at), (I) S100A8 (Affymetrix IDs: 202917_at), (J) S100A9 (Affymetrix IDs: 203535_at), (K) S100B (Affymetrix IDs: 209686_at), (M) S100 P (Affymetrix IDs: 204351_at), (N) S100A2 (Affymetrix IDs: 204268_at), and (O) S100A6 (Affymetrix IDs: 217728_at) are plotted for all GC patients (n = 876).

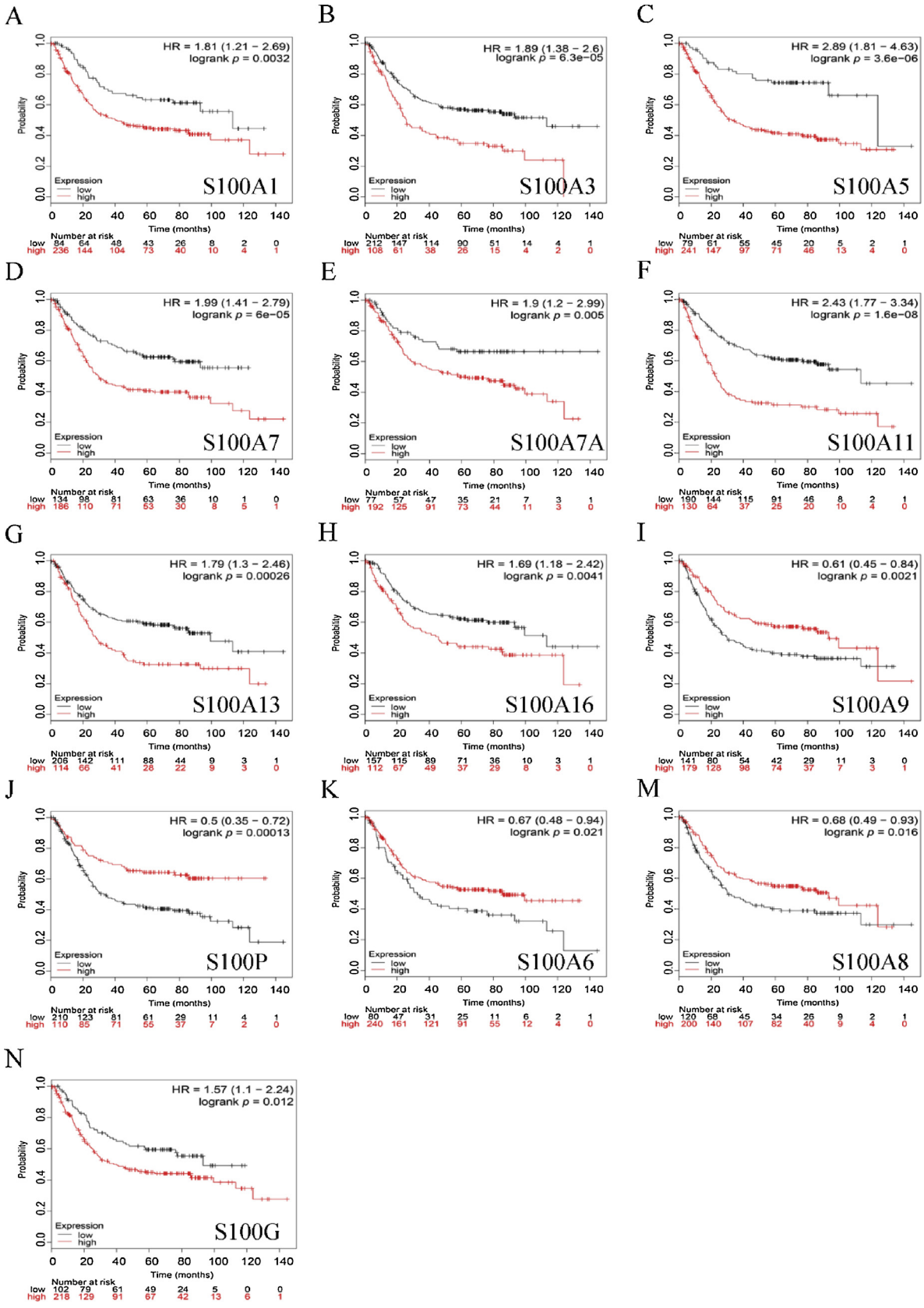

Fig. 2. Survival curves of (A) S100A1 (Affymetrix IDs: 205334_at), (B) S100A3 (Affymetrix IDs: 206027_at), (C) S100A5 (Affymetrix IDs: 207763_at), (D) S100A7 (Affymetrix IDs: 205916_at), (E) S100A7A (Affymetrix IDs: 232170_at), (F) S100A11 (Affymetrix IDs: 200660_at), (G) S100A13 (Affymetrix IDs: 202598_at), (H) S100A16 (Affymetrix IDs: 227998_at), (I) S100A9 (Affymetrix IDs: 203535_at), (J) S100 P (Affymetrix IDs: 204351_at), (K) S100A6 (Affymetrix IDs: 217728_at), (M) S100A8 (Affymetrix IDs: 202917_at) and (N) S100 G (Affymetrix IDs: 207885_at) are plotted for intestinal type GC patients (n = 336).

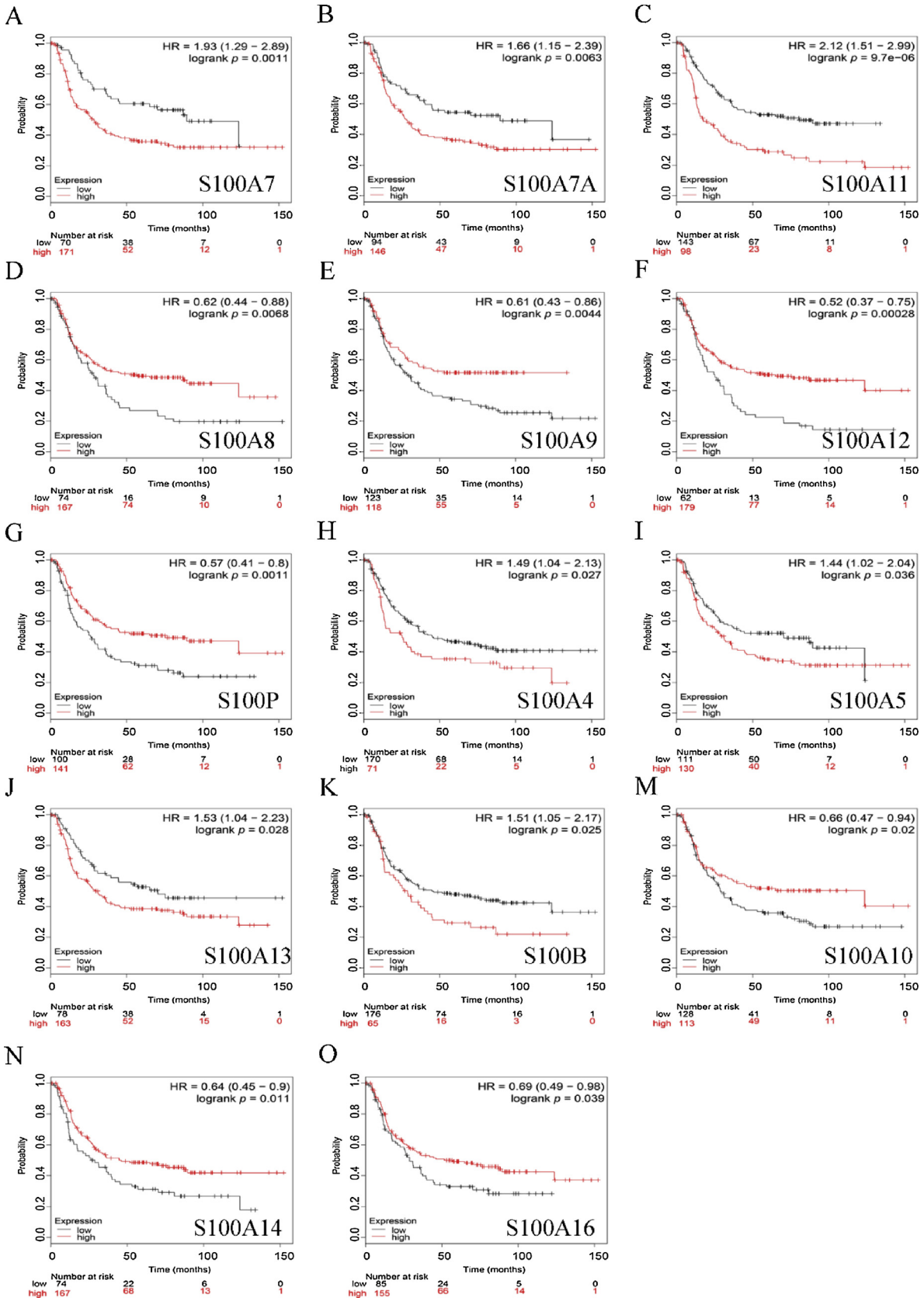

Fig. 3. Survival curves of (A) S100A7 (Affymetrix IDs: 205916_at), (B) S100A7A (Affymetrix IDs: 232170_at), (C) S100A11 (Affymetrix IDs: 200660_at), (D) S100A8 (Affymetrix IDs: 202917_at), (E) S100A9 (Affymetrix IDs: 203535_at), (F) S100A12 (Affymetrix IDs: 205863_at), (G) S100 P (Affymetrix IDs: 204351_at), (H) S100A4 (Affymetrix IDs: 203186_s_at), (I) S100A5 (Affymetrix IDs: 207763_at), (J) S100A13 (Affymetrix IDs: 202598_at), (K) S100B (Affymetrix IDs: 204351_at), (M) S100A10 (Affymetrix IDs: 200872_at), (N) S100A14 (Affymetrix IDs: 218677_at), and (O) S100A16 (Affymetrix IDs: 227998_at) are plotted for diffuse type GC patients (n = 248).

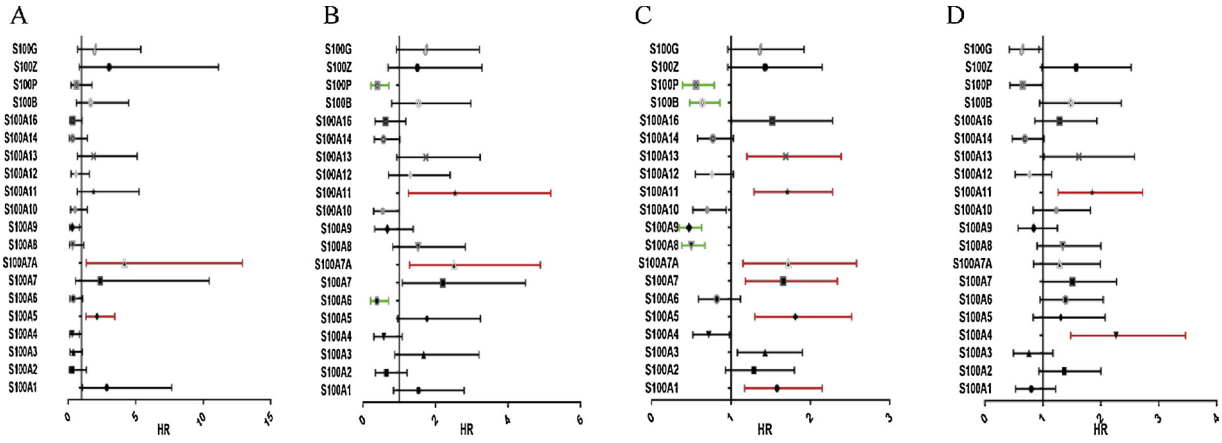

Fig. 4. Prognostic HRs of individual S100 members with different clinical stages of GC patients. (A) Stage I, (B) Stage II, (C) Stage III, (D) Stage IV.

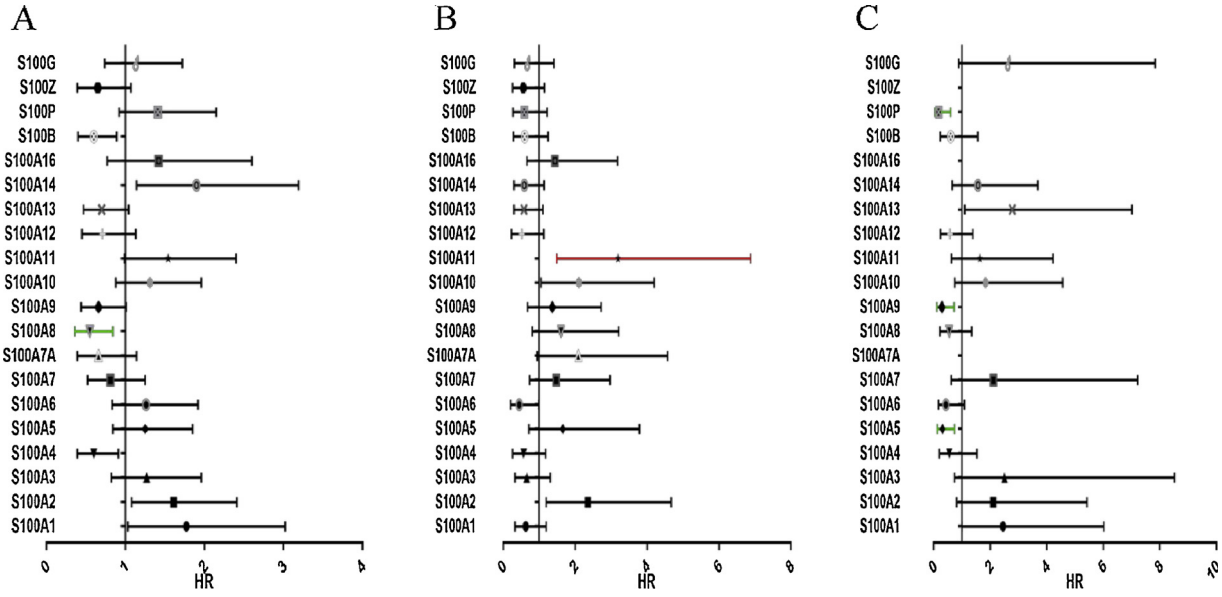

Fig. 5. Prognostic HRs of individual S100 members with different differentiation grades of GC patients. (A) Poorly differentiated, (B) Moderately differentiated, (C) Well differentiated.

1.15–2.58, p = 0.0078), S100A11 (HR = 1.71, 95%CI: 1.29–2.28, p = 2e-04) and S100A13 (HR = 1.69, 95%CI: 1.2–2.39, p = 0.0026) were related with lower OS in stage III GC. Only S100A4 (HR = 2.26, 95%CI: 1.48–3.46, p = 0.00011) and S100A11 (HR = 1.85, 95%CI: 1.26–2.72, p = 0.0015) were significantly associated with survival in stage IV GC. As we can see from Fig. 5, S100A8 (HR = 0.55, 95%CI: 0.36-0.84, p = 0.0054) mRNA elevated expression was associated with better prognosis in poorly differentiated GC. S100A11 high mRNA expression was correlated to poor survival in moderately differentiated GC (HR = 3.2, 95%CI: 1.49–6.88, p = 0.0017). In well differentiated GC, high mRNA expression of S100A5 (HR = 0.31, 95%CI: 0.13-0.73, p = 0.0049), S100A9 (HR = 0.29, 95%CI: 0.11-0.72, p = 0.0048) and S100P (HR = 0.17, 95%CI: 0.05-0.6, p = 0.0019) were linked to better prognosis. Fig. 6 has shown that mRNA expression of S100B (HR = 0.59, 95%CI: 0.45-0.77, p = 6.5e-05) and S100P (HR = 0.67, 95%CI: 0.51-0.87, p = 0.0026) were associated with better prognosis in HER2 positive GC. However, S100A5 (HR = 1.59, 95%CI: 1.21–2.08, p = 0.0071), S100A7 (HR = 1.79, 95%CI: 1.34–2.4, p = 7.1e-05), S100A7A (HR = 1.69, 95%CI: 1.17–2.46, p = 0.0051) and S100A11 (HR = 1.88, 95%CI: 1.38–2.56, p = 4.6e-05) were correlated to worse OS in HER2 positive GC. In HER2 negative GC, S100A6 (HR = 0.72, 95%CI: 0.56-0.91, p = 0.0071), S100A8 (HR = 0.55, 95%CI: 0.44-0.69, p = 1.8e-07), S100A9 (HR = 0.53, 95%CI: 0.42-0.66, p = 1.5e-08), S100A14 (HR = 0.73, 95%CI: 0.58-0.92, p = 0.0079), S100B (HR = 0.74, 95%CI: 0.59-0.93, p = 0.0084) and S100P (HR = 0.74, 95%CI: 0.59-0.93, p = 0.0084) were linked to better OS, whereas S100A3 (HR = 1.36, 95%CI: 1.09–1.7, p = 0.069), S100A5 (HR = 1.73, 95%CI: 1.38–2.16, p = 1.3e-06), S100A7 (HR = 1.87, 95%CI: 1.41–2.46, p = 7.9e-06), S100A7A (HR = 1.57, 95%CI: 1.12–2.19, p = 0.0082), S100A11 (HR = 1.81, 95%CI: 1.44–2.27, p = 1.7e-07) and S100A13 (HR = 1.68, 95%CI: 1.31–2.16, p = 4.2e-05) were associated with worse OS. As from Fig. 7, S100 P mRNA elevated expression was associated with better prognosis in GC patients with surgery alone (HR = 0.63, 95%CI: 0.45-0.87, p = 0.0045). However, the mRNA expression of S100A5 (HR = 1.92, 95%CI: 1.31–2.81, p = 0.00063), S100A7A (HR = 1.58, 95%CI: 1.15–2.16, p = 0.0041) and S100A11 (HR = 1.49, 95%CI: 1.11–2.01, p = 0.0077) were correlated to worse survival in GC patients with surgery alone. In GC patients with 5 FU based adjuvant, high mRNA expression of S100A1 (HR = 0.56, 95%CI: 0.39-0.8, p = 0.0014) and S100B (HR = 0.53, 95%CI: 0.36-0.78, p = 0.00086) were related to better prognosis, whereas S100A2 (HR = 1.75, 95%CI: 1.22–2.51, p = 0.002), S100A3 (HR = 1.76, 95%CI: 1.24–2.5, p = 0.0014), S100A5 (HR = 2.07, 95%CI: 1.39–3.08, p = 0.00024), S100A10 (HR = 1.81, 95%CI: 1.28–2.57, p = 0.00076) and S100A12 (HR = 2.12, 95%CI: 1.48–3.04, p = 2.5e-05) were linked to worse survival. Only S100P (HR = 0.15, 95%CI:

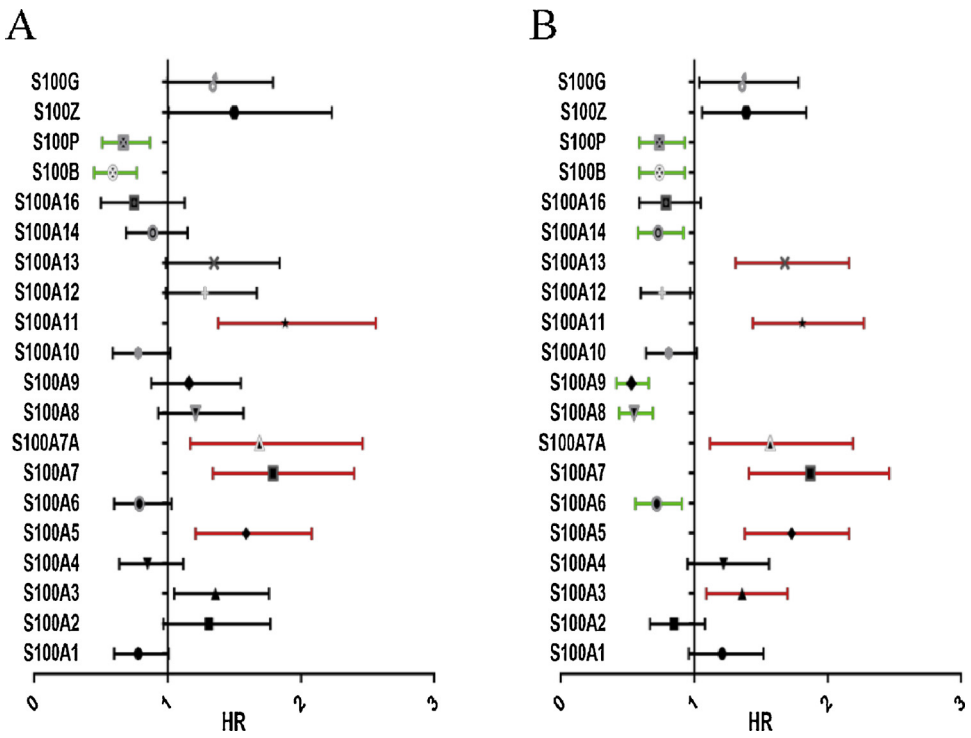

Fig. 6. Prognostic HRs of individual S100 members with different HER2 status of GC patients. (A) HER2 positive, (B) HER2 negative.

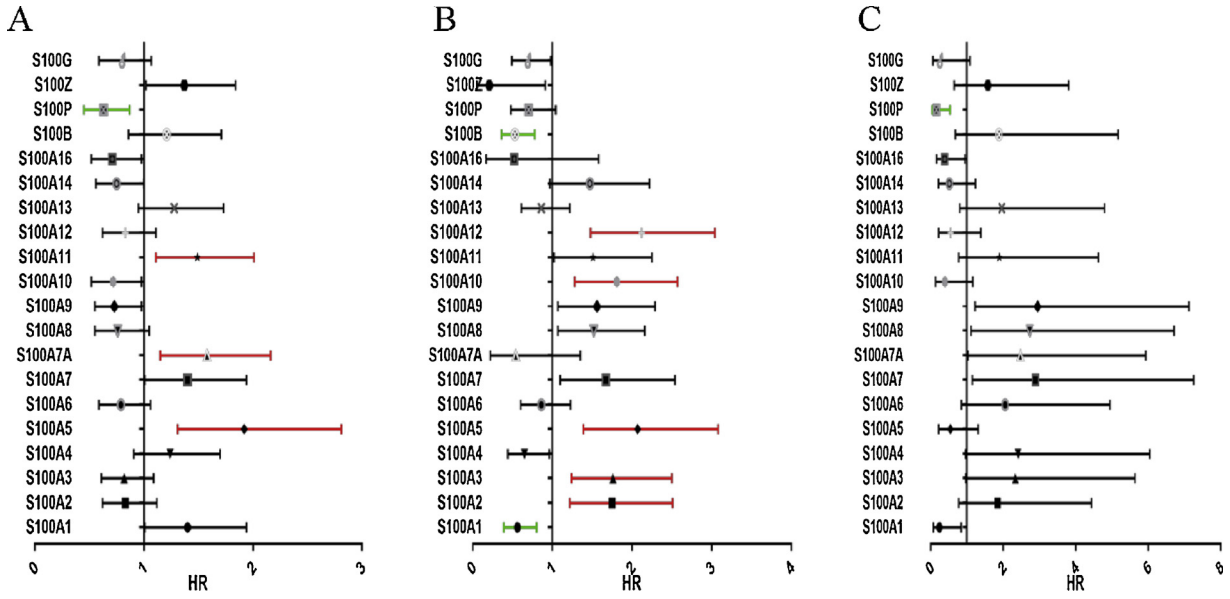

Fig. 7. Prognostic HRs of individual S100 members with different clinical treatments of GC patients. (A) Surgery alone, (B) 5 FU based adjuvant, (C) Other adjuvant.

0.04-0.53, p = 6e-04) mRNA expression level was correlated with prognosis in GC patients with the other adjuvant chemotherapy.

4. Discussion

In our study, we assessed the expression level of 20 S100 members and its prognostic value in GC. Among them, 12 members were significantly correlated with prognosis and 2 members were modestly associated with survival. Dysregulation of S100 expression is a common occurrence in numerous human cancers. The aberrant expression levels of S100 is associated with progressive diseases, but the molecular mechanisms of how S100 proteins contribute to disease aggression are not understood. Among the 14 S100 family members mentioned before, S100A2, S100A3, S100A5, S100A7, S100A7A, S100A11, S100A13, S100Z and S100 G exhibit altered expressions in several cancer [35,36]. Our results confirmed that high mRNA expression of these members was positively correlated with poor survival in all GC patients. However, there is sparse information regarding the role of S100A2, S100A5, S100A7, S100A7A, S100A13, S100Z and S100 G in GC, we selectively discuss the other members in this study.

S100A3, a protein related with the development of hair follicle, had been proven to be upregulated and play important roles in the tumorigenesis and progression of several cancers [37–40]. In GC, S100A3 was overexpressed and correlated with the poor differentiation and high TNM stage of GC cells [21]. Here, our results supported that elevated mRNA expression of S100A3 may indicate worse outcome of GC

patients.

S100A4 is implicated in the regulation of a broad spectrum of intracellular and extracellular biological effects such as cell motility, survival, differentiation and contractility. Increased expression of S100A4 has been found in several cancer types, its expression in non-metastatic cell lines was shown to trigger a more metastatic phenotype [41,42], while S100A4 downregulation was correlated with a lower metastatic capacity [43,44]. In addition, transgenic animal studies have revealed positive correlations between S100A4 and both metastasis and tumor progression [45,46]. Elevated expression of S100A4 is more frequently observed in patients with advanced GC, positive lymph node metastasis and peritoneal dissemination [47,48]. Clinical studies have convincingly confirmed that significant expression of S100A4 in GC is indicative of poor prognosis [49–51]. Our data suggested that high mRNA expression of S100A4 was correlated with worse OS in patients with stage IV GC, but we failed to find any association between the S100A4 expression and prognosis in all GC patients. The results indicated that S100A4 may serve as a promising indicator of the aggressiveness of GC in clinicopathological practice. Zhao et al. reported that S100A4 was highly expressed in diffuse-type carcinoma compared to that in intestinal type [51]. We reported a similar result, high expression of S100A4 was correlated modestly with poor survival in diffuse-type GC, but not in intestinal-type GC.

S100A6 is abundantly expressed in proliferating but not quiescent fibroblasts cells [52]. High expression of S100A6 has been testified to be linked to the progression and invasion of several human cancers [53–55]. Overexpression of S100A6 protein is correlated with poor prognosis in GC patients [22]. However, contrary to our expectation, high expression of S100A6 in GC was correlated moderately with better OS in this study. There are two possible explanations for this controversial result: first, we attained this result by the retrospective Kaplan-Meier plotter database and second study of S100A6 has concentrated largely on in vitro systems and further clinical trials are required to authenticate the findings.

S100A8 and S100A9 are initially found in myeloid cells and naturally form a stable heterodimer, involving in myeloid cell differentiation [56]. Association among S100A8 and S100A9 expression, clinicopathological features and patient survival varies in different cancer types. In lung cancer [36,57] and invasive ductal carcinoma of breast cancer [35,58], overexpression of S100A8 and S100A9 has been implicated in the development and progression of cancer [59]. In thyroid cancer [60], expression of S100A8 and S100A9 in cancer cells is critical for dedifferentiation. Exogenous S100A8 and S100A9 promotes invasion and migration through p38 Mitogen-Activated Protein Kinase-dependent NF-κB activation in GC cells [61]. However, S100A8 and S100A9 detected by immunohistochemistry was specifically expressed in inflammatory cells infiltrating chronic gastritis tissues and GC tissues [23]. S100A9-positive inflammatory cells in GC tissues are correlated with early stage of GC and better prognosis, whereas the number of S100A8-positive cells did not significantly associated with patient survival [23]. According to our results, S100A8 and S100A9 were positively correlated with better OS for all GC, especially in diffuse type, HER2 negative and stage III GC patients.

S100A11 is considered as a potential tumor suppressor gene which modulates signaling pathways for Ca^{2+}-induced growth arrest in human keratinocytes [62,63]. However, S100A11 is significantly upregulated in cancers, suggesting a progressive role implicated in cancer cell growth [64,65]. In GC, S100A11 expression was upregulated and related with the development of lymph node metastasis [24]. In this study, our finding confirmed that S100A11 was significantly correlated with lower OS for all GC patients, especially in stage II-IV and moderately differentiated GC.

S100B is preferentially expressed in Schwann cells of the peripheral nervous system and extraneuronally in adipocytes, chondrocytes and melanocytes [66,67] and is involved in modulating enzyme activities, cell growth and differentiation [68,69]. S100B acts a prognostic role in the majority of brain metastasis of melanoma [70]. Calcyclin-binding protein/Siah-1-interacting protein (CacyBP/SIP), a target protein of the S100 family, which contains S100A1, S100A6, S100A12, S100B and S100 P, has been identified as a potential inhibitor of cell proliferation and invasion in the GC cell through the down-regulation of β-catenin and transcriptional activation of Tcf/LEF [71]. In accordance with this, our results confirmed that elevated mRNA expression of S100B was positively associated with better survival in all GC patients. Unexpectedly, high mRNA expression of S100B was correlated modestly with worse survival in diffuse type GC, indicating that S100B may play a pivotal role in diffuse type carcinogenesis.

S100 P was originally identified in human placenta [72], now it is becoming a promising marker in diagnosing and predicting cancers [26,73–75].S100 P is also expressed in GC [76,77] and appears to function to increase the growth and invasion of the cancer cells [78]. Ge et al. [25] reported that S100 P was overexpressed in GC compared with normal tissues and was related with TNM stage and poor survival. In contrast, Jia et al. [26] demonstrated that down-regulated expression of S100 P in GC in comparison with normal control. Patients with S100P-positive cancers showed a better prognosis than those with negative S100 P expression. In the present study, high expression level of S100 P was a positive prognostic marker in GC patients. S100 P enhanced oxaliplatin chemosensitivity in GC cell lines via increasing drug inflow, which imply that S100 P may be a predictor of better prognosis in GC patients who receive adjuvant chemotherapy with oxaliplatin [79]. Consistent with this result, our finding showed that the high expression of S100 P mRNA was positively associated with longer OS in GC patients with other adjuvant chemotherapy rather than 5 FU based adjuvant.

HER2 amplification and overexpression have been reported in numerous human cancers, including breast cancer, gastric carcinoma, salivary gland tumor and ovarian cancer [80]. Overexpression and amplification of HER2 is commonly correlated with increased tumor aggressiveness, high recurrence rates and poor survival [81]. The S100 protein family is the largest subfamily of EF-hand calcium-binding proteins, and several members have been shown to be overexpressed and related with tumor invasion, progression and prognosis [35,36]. S100A7 can interact with HER2 signaling pathway by distinct and specific phosphorylation of tyrosine residues of EGFR/HER2, SHP2 and Src in breast cancer cells [82]. S100A14 expression is strongly associated with HER2 expression in breast cancer tissues and S100A14 can bind directly to and phosphorylate HER2 in a Ca^{2+}-dependent manner and consequently promote cell growth [83]. At present, there are no reports indicating a direct correlation between S100 proteins and HER2 status in GC. In our study, expression of S100A3, S100A5, S100A6, S100A7, S100A7A, S100A8, S100A9, S100A11, S100A13, S100A14, S100B and S100 P correlated with HER2 status of GC patients. S100B and S100 P were positively associated with better prognosis in HER2 positive GC. However, S100A5, S100A7, S100A7A and S100A11 were correlated to worse survival in HER2 positive GC. In HER2 negative GC, S100A6, S100A8, S100A9, S100A14, S100B and S100 P were strongly associated with better OS, whereas S100A3, S100A5, S100A7, S100A7A, S100A11 and S100A13 were correlated with worse OS.

Surgical resection remains the primary curative treatment option in GC, patient survival is largely related to stage, with a high percentage of patients with metastatic disease at presentation [84]. Despite the advantage of adjuvant therapy has been evidently demonstrated, no general agreement has been reached on the ideal treatment choice. The narrow therapeutic index of adjuvant chemotherapy requires a careful evaluation of expected benefits and risks for individual patients [84]. Therefore, identification of promising molecular prognostic markers for tumor aggression and survival is of great significance in GC than in other malignancies, and their detection in serum or small biopsy specimens would help guide clinical decision-making with regards to cancer treatment and outcomes. In present study, we assessed the correlation of the prognostic values of S100 members with clinical

treatments of GC. The expression of S100A5, S100A7A and S100A11 correlated with poor survival in GC patients with surgery alone, whereas only S100 P was related with better prognosis in GC patients with surgery alone. In GC patients with 5 FU based adjuvant, increased expression of S100A2, S100A3, S100A5, S100A10 and S10012 were associated with lower OS, while S100A1 and S100B were linked with longer OS. In GC patients with the other adjuvant chemotherapy, only S100 P mRNA expression level was associated with better prognosis.

In our study, several potential limitations should be considered when interpreting the results. First, due to the incomplete clinical information of GC from the database and the small sample size, multivariate analysis by COX regression which can correct the confounding factors couldn't be achieved in this database. Second, our results are based on the bioinformatics analysis of GEO. Therefore, further experiments must be designed and performed to confirm our results.

In summary, the prognostic values of 20 members of the S100 family in GC patients was determined by the KM plotter database. Among them, 12 members were strongly correlated with survival in GC patients. The prognostic value of the S100 protein should be further assessed in clinical trials. These findings will be helpful for exploring the relationship between proteins and diseases and their functions in distinct signaling pathways. Our study offers new insights into the contribution of S100 members to GC progression and might promote development of S100 targeted reagents for treating GC.

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Conflict of interest

The authors report no conflict of interest in this work.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study, formal consent is not required.

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