Research Article

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Distinct expression and prognostic value of MS4A in gastric cancer

Abstract: Gastric cancer has high malignancy and early metastasis, which lead to poor survival rate. In this study, we assessed the expressions and prognostic values of MS4A family, a newly recently discovered family, by two online dataset, GEPIA and Kaplan Meier-plotter. From these results eight members, MS4A2, MS4A6, MS4A7, MS4A8, MS4A14, MS4A15, TMEM176A and TMEM176B showed positive expression in gastric cancer or normal tissues, and these genes were screened for further analysis of prognostic values. We observed that low mRNA expressions of MS4A2, MS4A7, MS4A14, MS4A15, TMEM176A and TMEM176B were correlated with better overall survival (OS) in all gastric cancer patients, while high mRNA expression of MS4A6 was observed to be associated with good prognosis. MS4A8's high mRNA level was correlated to better OS in diffuse gastric cancer patients. Further, we estimated prognostic values of MS4A family in gastric cancer patients with different clinic-pathological features, including clinical stages, differentiation level, lymph node status and HER2 status. Our results indicate that these eight MS4A members can estimate prognosis in patients with different pathological groups. In conclusion, MS4A family members are potential biomarkers, and may contribute to tumor progression in gastric cancer.

Keywords: Membrane-spanning 4-domains subfamily A; Gastric cancer; Prognosis; mRNA expression

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1 Introduction

Gastric cancer is one of the most frequent malignant tumor and the second leading cause of mortality from any type of cancer worldwide [1]. Because of its high malignancy and early metastasis, the 5-year overall survival is only about 30% to 50%. Although the comprehensive treatment of gastric cancer with surgery, radiotherapy and chemotherapy is constantly updated, the overall survival rate is yet not significantly improved. There is still a lack of specific therapeutic targets and independent prognostic indicators [2]. Therefore, there is an urgent need to develop methods that can inhibit the invasion and metastasis of gastric cancer, as well as indicators that can independently guide the prognosis.

Membrane-spanning 4-domains subfamily A (MS4A) belongs to transmembrane proteins and contains at least 16 members in human [3]. MS4A family members are homologous in amino acid sequences with similar chromosome location and protein structure. These genes are mainly expressed in lymphocytes and hematopoietic cells, operating as cell surface signaling and intracellular adapter proteins [4]. In recent years, with the in-depth study of the MS4A family members, it has been observed that MS4A proteins show abnormal expression and fulfil diverse functions in multiple solid tumor tissues [5-9]. However, studies of MS4A in tumor are in the initial stage, and the role of MS4A in gastric cancer still remains unknown.

In the present study, we analyzed MS4A family expression levels in gastric cancer, and screened 8 members that showed positive expression to analyze their prognostic values in gastric cancer using an online dataset. Seven of them were confirmed to be potential prognostic markers in gastric cancer.

2 Methods

Expression and prognostic values of MS4As family were analyzed using two online dataset, Gene Expression Pro-

filing Interactive Analysis (GEPIA) and Kaplan Meier-plotter dataset (http://kmplot.com/analysis/). GEPIA was an interactive web server for estimating the mRNA expression data from 9,736 tumors and 8,587 normal samples in the Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) dataset projects [10]. The |Log$_2$FC| cutoff of the expression of proposed biomarker was 1. All boxplot analysis used log2(TPM + 1) for log-scale.

Kaplan Meier-plotter database can analyze prognostic values of gene mRNA expression in breast, gastric, lung and ovarian cancer patients, and also miRNA expression in liver and breast cancer patients [11]. Samples with gene expression data and prognosis information used in Kaplan Meier-plotter dataset are downloaded from TCGA, EGA and GEO (Affymetrix microarrays only). The database is handled by a PostgreSQL server, which integrates gene expression and clinical data simultaneously. So far, a number of genes have been identified and validated by KM plotter in these four types of cancer [12-15]. In this on line dataset, clinical data from 876 gastric cancer patients including Lauren classification, clinical stage, differentiation, HER2 status and lymph node status were collected. The Affymetrix IDs of MS4As were entering into the web (http://kmplot.com/analysis/index.php?p=service&cancer=gastric), and then data were compared through a Kaplan-Meier survival plot. The patient samples were split into two groups by median. The hazard ratio (HR) with 95% confidence intervals (95% CI) and P value were calculated by a PostgreSQL server. *P* < 0.05 was considered to be a significant difference.

3 Results

3.1 Differential expression of MS4As between tumor and normal tissues in gastric cancer

This study was set out with the aim of assessing MS4As prognosis values in gastric cancer. First, we excluded MS4A family members which were negative or nearly negative in gastric cancer tissues. An online tool, GEPIA which was based on TCGA and GTEx dataset for transcriptomic analysis, was used to investigate the mRNA expression level of MS4A family in gastric cancer [10]. Analysis results demonstrated that expressions of MS4A1, MS4A3, MS4A4, MS4A5, MS4A10, MS4A12, MS4A13 and MS4A18 were negative or nearly negative, while MS4A2, MS4A6, MS4A7, MS4A8, MS4A14, MS4A15, TMEM176A and TMEM176B expressions were positive in gastric cancer

or paracancerous tissues. The results of these MS4A members' expression are shown in Figure 1. From the boxplot, we confirmed that MS4A2 mRNA level decreased in gastric cancer tissues in cooperation to normal tissues (Fig. 1A). By contrast, MS4A6, MS4A7 and MS4A15 mRNA levels increased in gastric cancer tissues (Fig. 1B, C and F). Notably, TMEM176A and TMEM176B mRNA levels were observed to be up-regulated with statistical significance in gastric cancer tissues (Fig. 1G and H). Based on these data, eight members were screened for further prognostic value analysis.

3.2 Prognostic value of MS4A family in gastric cancer

Prognostic roles of eight screened MS4A family were determined in www.kmplot.com. The valid Affymetrix IDs are as follows: 207496_at (MS4A2), 219666_at (MS4A6), 223344_s_at (MS4A7), 224355_s_at (MS4A8), 229510_at (MS4A14), 1564194_a_at (MS4A15), 218345_at (TMEM176A), 220532_s_at (TMEM176B). Figure 1 represents a survival curves plotted for all patients with gastric cancer (n = 876). From this data, low mRNA expression of MS4A2 was correlated with better OS in all gastric cancer [HR = 1.23, 95% CI: (1.03-1.47), P = 0.025], as well as MS4A7 [HR = 1.33, 95% CI: (1.05-1.68), P = 0.019], MS4A14 [HR = 1.25, 95% CI: (1.25-1.92), P<0.0001], MS4A15 [HR = 1.28, 95% CI: (1.04-1.59), P = 0.022], TMEM176A [HR = 1.49, 95% CI: (1.24-1.78), P<0.0001] and TMEM176B [HR = 1.64, 95% CI: (1.37-1.96), P<0.0001]. High mRNA expression of MS4A6 was observed to be associated with a good prognosis [HR = 0.72, 95% CI: (0.61-0.85), P = 0.00014]. MS4A8's high mRNA level was modestly correlated to better OS without statistical significance.

Furthermore, we estimated prognostic values of MS4As in gastric cancer patients with different Lauren classification, including intestinal, diffuse and mixed type. As shown in Figure 3, low MS4A2 mRNA level was associated with better OS in intestinal type gastric cancer patients [HR = 1.55, 95% CI: (1.12-2.14), P = 0.008], as well as MS4A7 [HR = 1.62, 95% CI: (1.12-2.33), P = 0.0092], MS4A14 [HR = 1.69, 95% CI: (1.17-2.43), P = 0.0048], MS4A15 [HR = 1.63, 95% CI: (1.13-2.35), P = 0.0088], TMEM176A [HR = 2.18, 95% CI: (1.57-3.03), P<0.0001] and TMEM176B [HR = 2.46, 95% CI: (1.72-3.51), P<0.0001]. Figure 4 shows the prognostic values of MS4As in diffuse type gastric cancer patients. From these data, patients with high MS4A2 [HR = 0.67, 95% CI: (0.47-0.94), P = 0.019] or MS4A8 [HR = 0.68, 95% CI: (0.47-0.99), P = 0.042] level show better OS, while patients with high MS4A14 [HR = 1.47, 95% CI: (1.02-2.13),
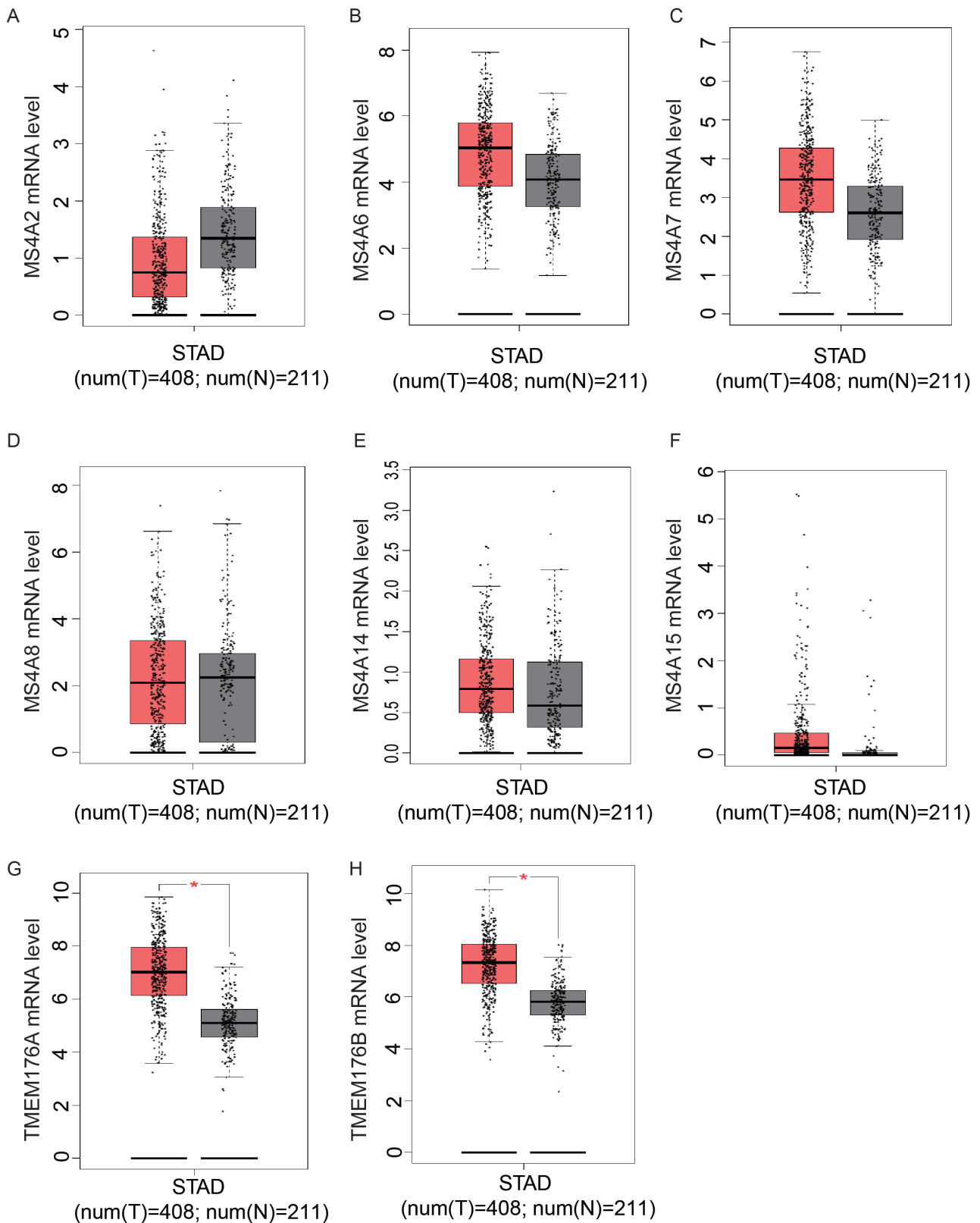
Figure 1: Analysis of MS4A mRNA level in human gastric cancer. The red and gray boxes represent cancer and normal tissues respectively. Compared with the normal tissues, MS4A2 (A) mRNA level decreases, while MS4A6 (B), MS4A7 (C) and MS4A15 (F) mRNA levels increase in gastric cancer tissues. There were only slight differences in MS4A8 (D) and MS4A14 (E) between gastric normal and cancer tissues. Notably, TMEM176A (G) and TMEM176B (H) mRNA level increased in gastric cancer tissues with statistically significant. (*P<0.01)
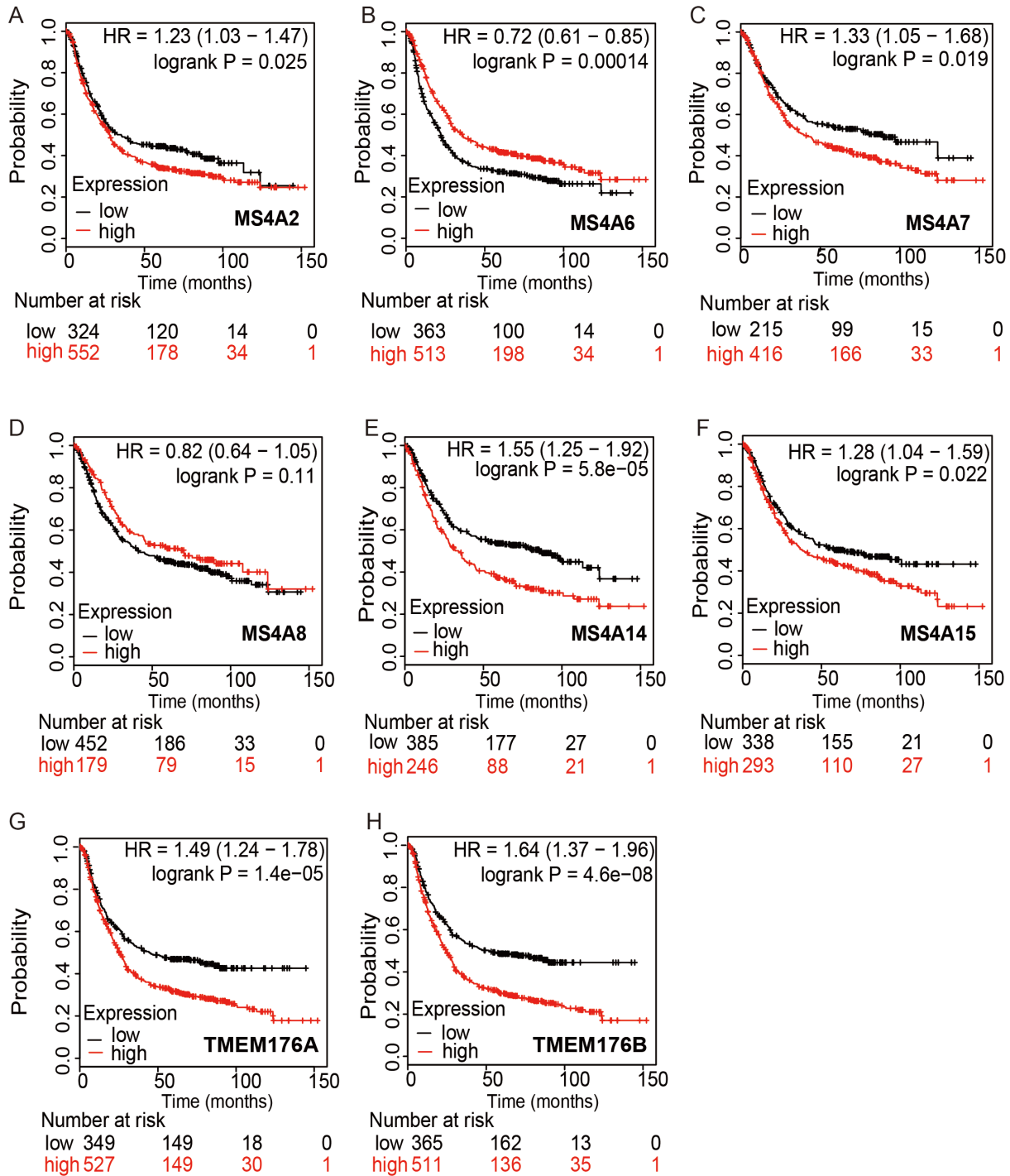
Figure 2: Prognostic roles of MS4A are determined in www.kmplot.com. The desired Affymetrix IDs are valid: 207496_at (MS4A2), 219666_at (MS4A6), 223344_s_at (MS4A7), 224355_s_at (MS4A8), 229510_at (MS4A14), 1564194_a_at (MS4A15), 218345_at (TMEM176A), 220532_s_at (TMEM176B). Survival curves are plotted for all gastric cancer patients (n = 876). From this data, high mRNA expression of MS4A6 (B), or low mRNA expression of MS4A2 (A) or MS4A7 (C) or MS4A14 (E) or MS4A15 (F) or TMEM176A (G) or TMEM176B (H) were correlated with better OS.
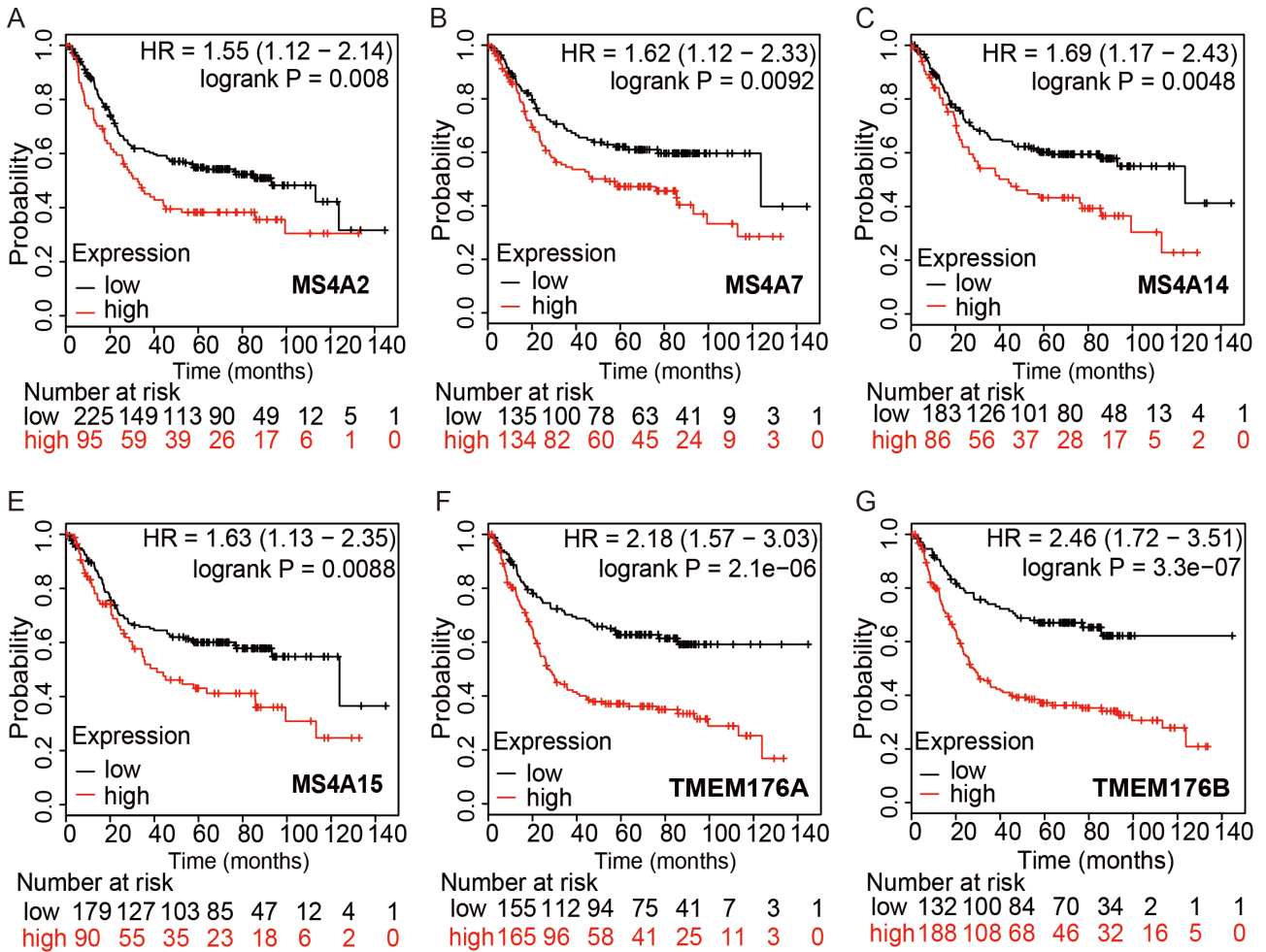
Figure 3: Prognostic roles of MS4A in the intestinal gastric cancer. Survival curves are plotted for intestinal gastric cancer patients (n = 336). Patients with low MS4A2 (A) level show better OS in intestinal gastric cancer, as well as MS4A7 (B), MS4A14 (C), MS4A15 (D), TMEM176A (E) and TMEM176B (F).

P = 0.04] or TMEM176B [HR = 1.51, 95% CI: (1.08-2.13), P = 0.016] show poorer OS in diffuse gastric cancer.

3.3 Prognostic roles of MS4A family in gastric cancer patients with different pathological characteristics

Next, we estimated prognostic values of MS4As in gastric cancer patients with different pathological characteristics, including clinical stages, differentiation level, lymph node status and HER2 status. Table 1 shows the results of prognostic value analysis for gastric cancer patients with different clinical stages. From these data, low mRNA level of MS4A2 was only correlated with a good prognosis in stage 3 gastric cancer patients [HR = 1.41, 95% CI: (1.04-1.92), P = 0.027]. MS4A6's high expression was correlated to better OS in stage 1 and 2 patients [stage 1: HR = 0.26,

95% CI: (0.09-0.77), P= 0.0091; stage 2: HR = 2.85, 95% CI: (1.12-7.25), P = 0.022]. MS4A7's low mRNA level was associated with good prognosis in stage 1, 3 and 4 patients [stage 1: HR = 0.3, 95% CI: (0.1-0.91), P = 0.024; stage 3: HR = 0.6, 95% CI: (0.41-0.87), P = 0.0066; stage 4: HR = 1.71, 95% CI: (1.08-2.71), P = 0.02]. Low expression of MS4A14 was correlated to good prognosis in stage 1 and 4 patients [stage 1: HR = 0.28, 95% CI: (0.07-1.05), P = 0.046; stage 4: HR = 1.85, 95% CI: (1.19-2.88), P = 0.0058]. Low expression of MS4A15 was associated with better OS in stage 1, 3 and 4 patients [stage 1: HR = 7.96, 95% CI: (2.44-25.94), P<0.0001; stage 3: HR = 1.59, 95% CI: (1.07-2.37), P = 0.021; stage 4: HR = 1.59, 95% CI: (1.06-2.39), P = 0.023]. Low mRNA level of TMEM176A was observed to be associated with a good prognosis in stage 1 and 3 [stage 1: HR = 18.63, 95% CI: (2.46-141.27), P<0.0001; stage 3: HR = 2.15, 95% CI: (1.49-3.1), P<0.0001]. Low mRNA level of TMEM176B was observed to be correlated to better OS in all stages gastric
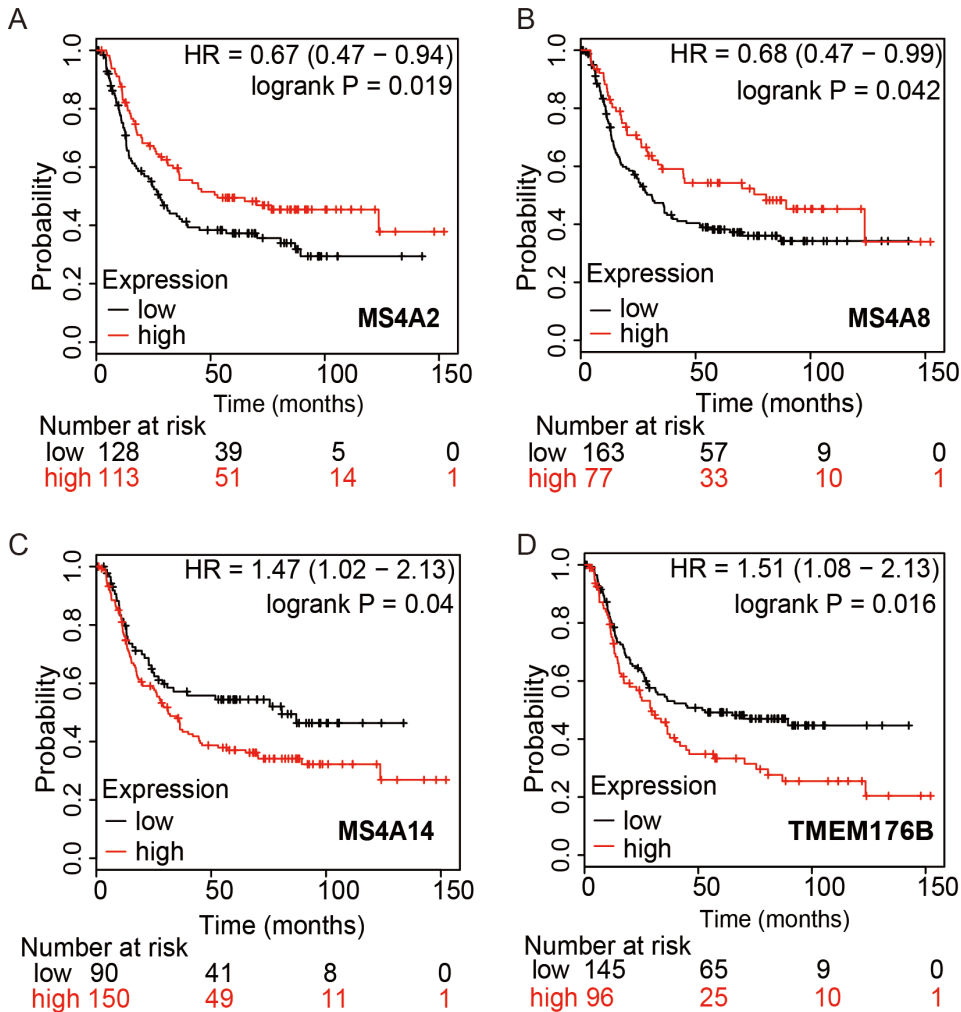
Figure 4: Prognostic roles of MS4A in diffuse gastric cancer. Survival curves are plotted for diffuse gastric cancer patients (n = 248). Patients with high MS4A2 (A) or MS4A8 (B) level show better OS, while patients with high MS4A14 (C) or TMEM176B (D) show poorer OS in diffuse gastric cancer.

cancer patients [stage 1: HR = 7.41, 95% CI: (2.1-26.11), P = 0.00026; stage 2: HR = 1.89, 95% CI: (1.03-3.46), P = 0.037; stage 3: HR = 1.89, 95% CI: (1.37-2.61), P<0.0001; stage 4: HR = 1.48, 95% CI: (1-2.17), P = 0.046.

Prognostic values of MS4As in different differentiation level are reported in Table 2. From these data, high MS4A2 expression was correlated to better OS in poorly differentiated gastric cancer patients [HR = 0.63, 95% CI: (0.4-0.97), P= 0.036]. High mRNA levels of MS4A14 [HR = 2.02, 95% CI: (1.04-3.92), P = 0.033] and TMEM176A [HR = 3.31, 95% CI: (1.37-7.98), P = 0.0048] were observed to be associated with a good prognosis in moderately differentiated patients. The rest members of MS4As were not associated with a prognosis in different differentiation level gastric cancer.

Table 3 reports the prognostic values of MS4As in different lymph node status. High mRNA level of MS4A6 was observed to be associated with better OS in lymph node

positive patients [HR = 1.37, 95% CI: (1.03-1.81), P = 0.028]. Low expressions of MS4A7 [HR = 1.45, 95% CI: (1.1-1.91), P = 0.0075], MS4A8 [HR = 0.69, 95% CI: (0.5-0.94), P = 0.018], MS4A14 [HR = 1.48, 95% CI: (1.14-1.93), P = 0.0036], TMEM176A [HR = 1.77, 95% CI: (1.35-2.31), P<0.0001] and TMEM176B [HR = 1.86, 95% CI: (1.43-2.41), P<0.0001] were correlated with a good prognosis in lymph node positive patients. High expressions of MS4A14 [HR = 2.6, 95% CI: (1.13-5.96), P = 0.019] and MS4A15 [HR = .45, 95% CI: (1.01-5.99), P = 0.042] were correlated with a good prognosis in lymph node negative patients.

Prognostic values of MS4As in gastric cancer patients with different HER2 status are shown in Table 4. Low mRNA levels of MS4A2 [HR = 1.32, 95% CI: (1-1.74), P = 0.052], MS4A7 [HR = 1.96, 95% CI: (1.3-2.96), P = 0.0012], MS4A14 [HR = 1.83, 95% CI: (1.16-2.91), P = 0.0087], MS4A15 [HR = 1.5, 95% CI: (1.03-2.18), P = 0.032] and TMEM176B [HR = 0.62, 95% CI: (0.46-0.85), P = 0.003] were correlated to

Table 1: Correlation of MS4A mRNA level with clinical stages of gastric cancer patients.

MS4A	Clinical stages	Cases	HR	95% CI	P
MS4A2	1	69	0.49	0.17-1.41	0.18
	2	145	1.9	0.98-3.7	0.053
	3	319	1.41	1.04-1.92	0.027
	4	152	0.75	0.51-1.11	0.15
MS4A6	1	69	0.26	0.09-0.77	0.0091
	2	145	2.85	1.12-7.25	0.022
	3	319	0.68	0.5-0.92	1.30E-02
	4	152	1.15	0.78-1.68	0.48
MS4A7	1	69	0.3	0.1-0.91	0.024
	2	145	1.69	0.88-3.25	0.11
	3	319	0.6	0.41-0.87	0.0066
	4	152	1.71	1.08-2.71	0.02
MS4A8	1	69	1.55	0.52-4.62	0.43
	2	145	1.31	0.69-2.48	0.41
	3	319	0.7	0.48-1.01	0.058
	4	152	0.74	0.46-1.19	0.21
MS4A14	1	69	0.28	0.07-1.05	0.046
	2	145	1.66	0.89-3.12	0.11
	3	319	1.51	0.94-2.44	0.086
	4	152	1.85	1.19-2.88	0.0058
MS4A15	1	69	7.96	2.44-25.94	<0.0001
	2	145	0.67	0.34-1.31	0.24
	3	319	1.59	1.07-2.37	0.021
	4	152	1.59	1.06-2.39	0.023
TMEM176A	1	69	18.63	2.46-141.27	<0.0001
	2	145	1.66	0.9-3.05	0.1
	3	319	2.15	1.49-3.1	<0.0001
	4	152	1.39	0.94-2.06	0.094
TMEM176B	1	69	7.41	2.1-26.11	0.00026
	2	145	1.89	1.03-3.46	0.037
	3	319	1.89	1.37-2.61	<0.0001
	4	152	1.48	1-2.17	0.046

HER2 positive patients. Low mRNA expressions of MS4A14 [HR = 1.64, 95% CI: (1.26-2.14), P = 0.00019], MS4A15 [HR = 1.35, 95% CI: (1.04-1.76), P = 0.024], TMEM176A [HR = 1.55, 95% CI: (1.23-1.95), P = 0.00019] and TMEM176B [HR = 1.62, 95% CI: (1.29-2.03), P<0.0001] were correlated to HER2 negative patients. However, high expression of MS4A6 was found to be associated with better OS in HER2 negative patients [HR = 0.67, 95% CI: (0.53-0.84), P = 0.00063].

Table 2: Correlation of MS4A mRNA expression with different differentiation level of gastric cancer patients.

MS4A	Differentiation	Cases	HR	95% CI	P
	poorly differentiated	166	0.63	0.4-0.97	0.036
MS4A2	moderately differentiated	67	0.51	0.23-1.11	0.085
	poorly differentiated	166	0.76	0.5-1.17	0.21
MS4A6	moderately differentiated	67	1.57	0.81-3.06	0.18
	poorly differentiated	166	0.7	0.43-1.16	0.17
MS4A7	moderately differentiated	67	1.85	0.95-3.62	0.067
	poorly differentiated	166	0.72	0.43-1.22	0.22
MS4A8	moderately differentiated	67	1.27	0.65-2.47	0.49
	poorly differentiated	166	1.32	0.8-2.17	0.27
MS4A14	moderately differentiated	67	2.02	1.04-3.92	0.033
	poorly differentiated	166	1.38	0.83-2.3	0.22
MS4A15	moderately differentiated	67	1.33	0.69-2.56	0.39
	poorly differentiated	166	0.72	0.47-1.11	0.13
TMEM176A	moderately differentiated	67	3.31	1.37-7.98	0.0048
	poorly differentiated	166	0.67	0.43-1.05	0.078
TMEM176B	moderately differentiated	67	1.84	0.92-3.67	0.079

Table 3: Correlation of MS4A mRNA level with different lymph node status of gastric cancer patients.

MS4A	Lymph node status	Cases	HR	95% CI	P
MS4A2	negative	76	0.6	0.25-1.47	0.26
	positive	437	0.86	0.65-1.12	0.26
MS4A6	negative	76	0.49	0.21-1.12	0.086
	positive	437	1.37	1.03-1.81	0.028
MS4A7	negative	76	0.54	0.23-1.28	0.16
	positive	437	1.45	1.1-1.91	0.0075
MS4A8	negative	76	2.01	0.68-5.93	0.2
	positive	437	0.69	0.5-0.94	0.018
MS4A14	negative	76	2.6	1.13-5.96	0.019
	positive	437	1.48	1.14-1.93	0.0036
MS4A15	negative	76	2.45	1.01-5.99	0.042
	positive	437	1.25	0.93-1.67	0.13
TMEM176A	negative	76	2.17	0.95-5.43	0.058
	positive	437	1.77	1.35-2.31	<0.0001
TMEM176B	negative	76	2.1	0.85-5.2	0.1
	positive	437	1.86	1.43-2.41	<0.0001

Table 4: Correlation of MS4A mRNA level with different HER2 status of gastric cancer patients.

MS4A	HER2 status	Cases	HR	95% CI	P
	negative	641	1.25	0.98-1.6	0.076
MS4A2	positive	425	1.32	1-1.74	0.052
	negative	641	0.67	0.53-0.84	0.00063
MS4A6	positive	425	0.84	0.65-1.09	0.19
	negative	641	1.26	0.97-1.65	0.086
MS4A7	positive	425	1.96	1.3-2.96	0.0012
	negative	641	0.77	0.56-1.05	0.093
MS4A8	positive	425	0.69	0.46-1.02	0.06
	negative	641	1.64	1.26-2.14	0.00019
MS4A14	positive	425	1.83	1.16-2.91	0.0087
	negative	641	1.35	1.04-1.76	0.024
MS4A15	positive	425	1.5	1.03-2.18	0.032
	negative	641	1.55	1.23-1.95	0.00019
TMEM176A	positive	425	0.77	0.58-1.01	0.059
	negative	641	1.62	1.29-2.03	<0.0001
TMEM176B	positive	425	0.62	0.46-0.85	0.003

4 Discussion

In human, the MS4A family has been identified to have at least 16 members, namely: MS4A1-8, MS4A10, MS4A12-15, MS4A18, TMEM176A and TMEM176B. Most of the MS4A family members have 4-transmembrane structures. TMEM176A and TMEM176B sharing 16% of amino acids and similar structure with MS4A are attributed to this family. This superfamily is mostly expressed in lymphoid tissues [16]. However, recent studies showed that some members are expressed in nonlymphoid tissues, and fulfil diverse functions, including kidney, lung, heart, liver, etc [17]. The first question in this study sought to determine which MS4A family members show positive expressions in gastric cancer or paracancerous tissues. Based on our results, we confirmed that MS4A2, MS4A6, MS4A7, MS4A 8, MS4A14, MS4A15, TMEM176A and TMEM176B were positively expressed in gastric cancer or paracancerous tissues. Notably, MS4A6, MS4A7, MS4A15, TMEM176A and TMEM176B were up-regulated in gastric cancer tissues in comparison to paracancerous tissues, while MS4A2 was down-regulated in gastric cancer tissues. The aberrant expressions of these genes suggested that they could contribute to the progression of gastric cancer.

The prognostic values of these genes in gastric cancer were assessed by Kaplan Meier-plotter dataset. These results confirmed the association between gene mRNA expressions with OS of patients with gastric cancer. From these data, low mRNA expressions of MS4A2, MS4A7, MS4A14, MS4A15, TMEM176A and TMEM176B were correlated with better OS in all gastric cancer patients, while high mRNA expression of MS4A6 was observed to be associated with a good prognosis. MS4A8's high mRNA level was correlated to better OS in diffuse gastric cancer patients.

In 2017, Ly D, et al. analyzed the gene expression on microarray datasets of resected tumor samples from 128 early-stage non-small cell lung cancer (NSCLC) adenocarcinoma patients to gain insights into the immune networks that regulate and/or predict tumor progression. They prove that the expression of MS4A2 is an independent prognostic marker for early-stage lung cancer patient survival[18]. In our results, MS4A2 is also an independent prognostic marker in gastric cancer. MS4A7 (CFFM4) is an earlier discovered member in MS4A family. Gingras et al. proved that with the increase of monocyte differentiation the MS4A7 expression level increased significantly, suggesting that MS4A7 may be related to the differentiation of monocytes[19]. Several studies on MS4A8 revealed

that this MS4A member shows abnormal expression in prostate and colon cancers, and contributes to the progression of prostate cancer [20,21]. Compared with other members of the MS4A family, TMEM176A and TMEM176B were reported more frequently in tumors[22,23]. The latest reports revealed TMEM176A to be frequently methylated in human esophageal squamous cell cancer (ESCC) and colorectal cancer. TMEM176A is considered to be a potential tumor suppressor in ESCC. The methylation of TMEM176A may serve as a diagnostic and prognostic marker in ESCC and colorectal cancer [24,25]. In breast cancer, lymphoma, skin cancer and liver cancer tissues, TMEM176A and TMEM176B expression levels show significant differences between cancer and normal tissues, suggesting that these two genes may be considered as biomarkers for the diagnosis of related tumors [23]. In the present study, we prove that MS4A7, TMEM176A and TMEM176B may serve as prognostic markers in gastric cancer. Interestingly, TMEM176A and TMEM176B are up-regulated in gastric cancer, and the high levels of TMEM176A and TMEM176B indicate a good prognosis, suggesting that these two genes may contribute to the progression of gastric cancer. Although the MS4A family plays an important role in intracellular calcium disturbance, cell differentiation, and regulation of tumor cell behavior, the role and mechanism of this family in gastric cancer have not been studied. Based on the literature search of MS4A family mechanism, we speculate that the high expression of MS4A in gastric cancer may be regulated by CDX2 (caudal type homeobox 2) or EVI1 (ecotropic viral integration site 1) [6,26]. These two genes are important transcription factors involved in the regulation of cell differentiation and proliferation in cells and have been reported to regulate the expression of MS4A family members in a variety of tumors, thereby affecting the biological behavior of tumor cells [27-29]. Moreover, MS4A7 promotes monocyte differentiation through the p38MAPK pathway in monocytic leukemia [19]. At present, there are few studies on the mechanism of action of the MS4A family, which will also be the focus of our research in the future.

In conclusion, our present study is focused on abnormal expressions and prognostic values of MS4A family in gastric cancer. The findings of our study suggested that eight MS4A family members show positive expression in gastric or gastric cancer tissues, and were found to be associated with a prognosis in gastric cancer. The results of further analysis with clinic-pathological features indicate that these eight MS4A family members can estimate a prognosis in patients with different pathological groups. MS4A family members are potential biomarkers of gastric cancer, and may contribute to tumor progres-

sion. However, there is yet no research on physiological significance of MS4A family in gastric cancer, the specific function and mechanism of which need to be further elucidated.

Competing financial interests statement: The authors declare no competing financial interests.

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