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Original Article

The prognostic value of the high-mobility group box family mRNA expressions in gastric cancer

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Abstract: The high-mobility group box (HMGB) family represents a group of proteins that consists of HMGB1, HMGB2, HMGB3, and HMGB4. The HMGB proteins carry out various biological functions that play roles in various cancers, including gastric cancer (GC). However, to date, the prognostic value of HMGB proteins in GC has not been investigated. The present study assessed the association among the mRNA expressions of the four HMGB family members and examined GC patients' prognoses using a "Kaplan-Meier" (KM plotter) survival analysis. The gene expressions of the HMGB family and the OS data of 876 GC patients were obtained from the KM plotter database. It was found that higher HMGB1, HMGB2, and HMGB3 mRNA levels were significantly correlated with a better overall survival (OS) for the GC patients. Further analysis revealed that the mRNA levels of some HMGB members were significantly correlated with their clinical characteristics, including gender, Lauren histological classification, pathological grade, clinical stage, status of human epidermal growth factor receptor-2 (HER2), and the different treatments. These findings have unveiled some novel prognostic roles of the HMGB proteins in GC, which may lead to the development of a better approach for more accurate GC prognoses. Furthermore, these results may offer potential molecular targets for the development of therapeutic drugs for GC.

Keywords: Gastric cancer, high-mobility group box, overall survival, prognosis, Kaplan-Meier plotter

Introduction

Gastric cancer (GC) is among the main causes of cancer-related deaths around the world [1, 2]. Studies conducted over the past decades have shown that patients with GC have high rates of recurrence, ranging from 40-60%, and metastasis, and a low overall 5-year survival rate (approximately 20%), mainly due to gradual treatment resistance [1, 3, 4]. The exact mechanisms underlying the carcinogenesis and progress of GC remain unclear. Therefore, further insight into the underlying mechanisms and the identification of reliable prognostic predictors are urgently needed to improve the clinical outcomes of GC patients.

The high-mobility group box (HMGB) family is the most abundant protein family among the high-mobility group proteins (HMGs). They can regulate gene transcription and maintain genomic stability through interactions with nucleotides, transcription factors, and histones [5-7]. The HMGB family consists of the following four members: HMGB1, HMGB2, HMGB3, and HMGB4, and they are highly conserved. A number of recent studies have reported that the HMGB proteins participate in the progression of GC, including invasion, metastasis, and angiogenesis, and that abnormal expressions of the HMGB proteins are correlated with poor outcomes and GC patient chemoresistance [8-11]. To date, the prognostic values of the four HMGB members have not been reported.

The "Kaplan-Meier plotter" (KM plotter) has been extensively applied in medical research to determine the effects of gene expression on survival in nearly 21 cancer types. The KM plotter was established by analyzing the gene expression and survival data that were obtained from the Gene Expression Omnibus (GEO) database (www.ncbi.nlm.nih.gov/geo/) [12, 15-17]. Using the KM plotter survival analysis,

the correlations of the genes with overall survival (OS), relapse-free survival, and distant metastasis-free survival of various cancers have been identified, and some of these have been experimentally validated [12-14].

In the present study, we attempted to assess the relationship between the expressions of the HMGB family members and GC prognosis by conducting a KM plotter survival analysis.

Materials and methods

The online KM plotter database [15] (http://kmplot.com/analysis/) was adopted to identify the correlation between the mRNA expressions of the four HMGB members and OS. In the KM plotter analysis, OS was defined as the time period from the beginning of the diagnosis or treatment to death. The cancer patient data in the KM plotter database were obtained from the Cancer Biomedical Informatics Grid (caBIG, http://cabig.cancer.gov/, the microarray data for the samples had been published previously in the Cancer Genome Atlas (TCGA, http://cancergenome.nih.gov) cancer datasets, and the caArray project), and the GEO (http://www.ncbi.nlm.nih.gov/geo/) [16]. The clinical parameters of the GC human subjects in the KM plotter database were as follows: gender, Lauren classification, stages, differentiation grades, status of human epidermal growth factor receptor-2 (HER2), and treatment methods. At present, the KM plotter database was established using the gene expression and OS data for 1,065 GC patients obtained from the GEO (GSE22377, GSE14210 and GSE51105).

During the KM plotter analysis in this study, each HMGB family member (HMGB1, HMGB2, HMGB3, or HMGB4) was entered into the database (http://kmplot.com/analysis/index.php?p=service&cancer=gastric), and based on this, the KM survival plots were created. The GC patients whose genes of interest had higher mRNA expressions than the median levels were assigned to the high expression group, and the GC patients whose genes of interest had lower mRNA expressions than the median levels were assigned to the low expression group. Subsequently, the 95% confidence intervals (95% CI), hazard ratios (HR), and log rank *P* values were calculated and were made available on the KM plotter online website (http://kmplot.com/analysis/). A *P*-value of <0.01 was considered statistically significant.

Results

A Kaplan-Meier survival analysis of the HMGB family mRNA expressions in gastric cancer patients

In order to determine the association between the HMGB family mRNA expressions and OS, a KM plotter analysis was performed for the 876 patients with GC. Since the HMGB family has four members, the KM survival curves were plotted for HMGB1, HMGB2, HMGB3 and HMGB4, respectively, on the basis of the KM survival data in www.kmplot.com (**Figures 1-4**). As shown in **Figure 1**, OS curves were created for the 876 GC patients (**Figure 1A**), the 320 patients with the intestinal type of GC (**Figure 1B**), and the 241 patients with the diffuse type of GC (**Figure 1C**). It was found that a higher HMGB1 mRNA expression was significantly correlated with better OS in all the GC patients (HR: 0.57 [0.47-0.69], *P*=1.8e-09). Furthermore, a greater HMGB1 mRNA expression was significantly related to better OS in patients with the intestinal type of GC (HR: 0.44 [0.32-0.62], *P*=5.4e-07), but no significant association between the HMGB1 mRNA expression and OS was observed among the patients with the diffuse type of GC (HR: 0.64 [0.45-0.91], *P*=0.011).

Subsequently, KM survival curves were plotted for HMGB2 to evaluate the prognostic importance of the HMGB2 mRNA expression in GC. The results are illustrated in **Figure 2**. It was observed that higher HMGB2 mRNA expression levels were significantly correlated with better OS in all the GC patients (HR: 0.49 [0.4-0.6], *P*=1.1e-11; **Figure 2A**). These two histological data subtypes suggest that a higher HMGB2 mRNA expression level is significantly associated with favorable OS in patients with the intestinal type of GC (HR: 0.46 [0.33-0.64], *P*=1.7e-06; **Figure 2B**), as well as in patients with the diffuse type of GC (HR: 0.52 [0.35-0.78], *P*=0.0014; **Figure 2C**).

In plotting the KM survival curves for HMGB3 for the GC patients, a significant correlation between the HMGB3 mRNA expression and better OS was identified in all the GC patients (HR: 0.79 [0.66-0.94], *P*=0.0089; **Figure 3A**)

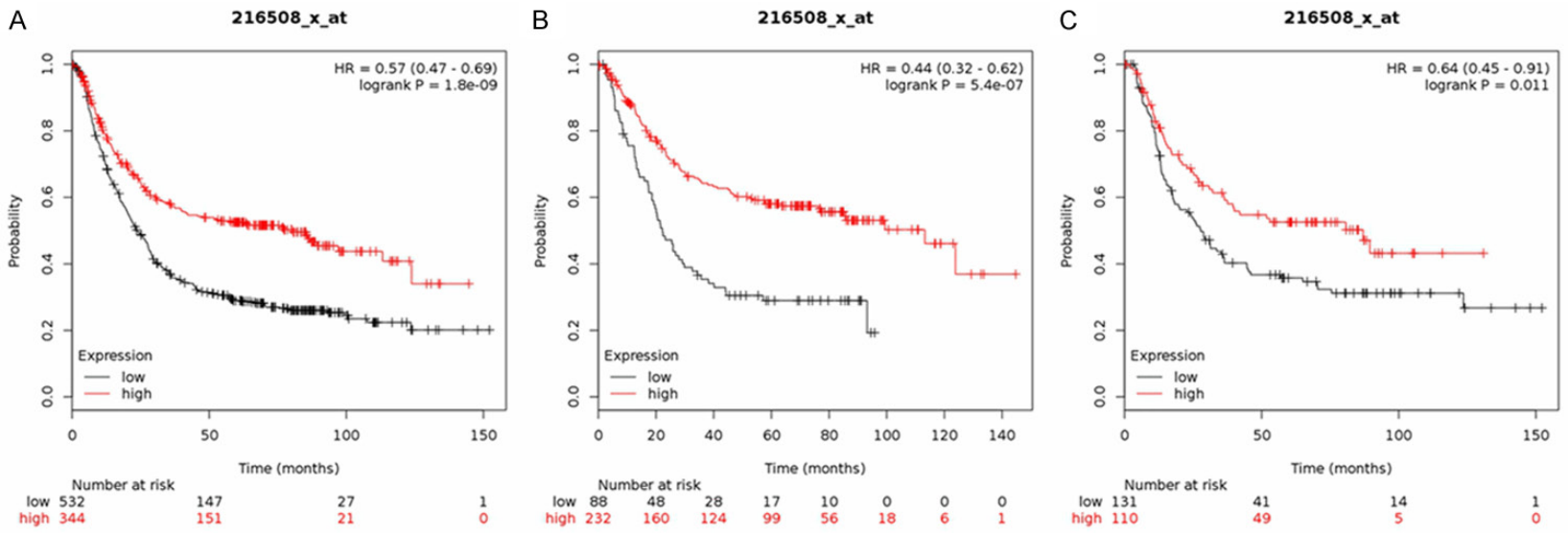

Figure 1. A Kaplan-Meier plotter analysis of the relationship between the *HMGB1* mRNA levels and OS in GC patients. The desired Affymetrix ID was valid: 216508_x_at (*HMGB1*). A. Kaplan-Meier survival curves were generated for all GC patients (*n*=876), regardless of the type; B. Kaplan-Meier survival curves were created for the GC patients with the intestinal type (*n*=320); C. Kaplan-Meier survival curves were generated for the GC patients with the diffuse type (*n*=241).

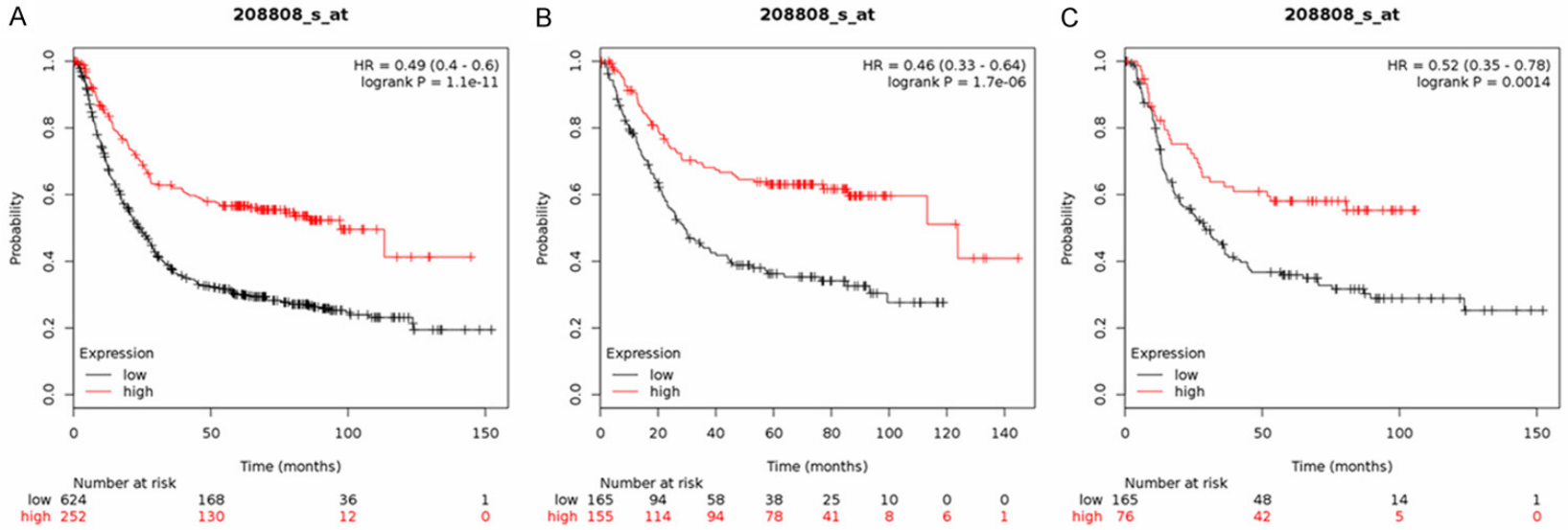

Figure 2. A Kaplan-Meier plotter analysis of the association between the *HMGB2* mRNA levels and OS in GC patients. The desired Affymetrix ID was valid: 208808_s_at (*HMGB2*). A. Kaplan-Meier survival curves were generated for all GC patients (*n*=876), regardless of the type; B. Kaplan-Meier survival curves were created for the GC patients with the intestinal type (*n*=320); C. Kaplan-Meier survival curves were generated for the GC patients diagnosed with the diffuse type (*n*=241).

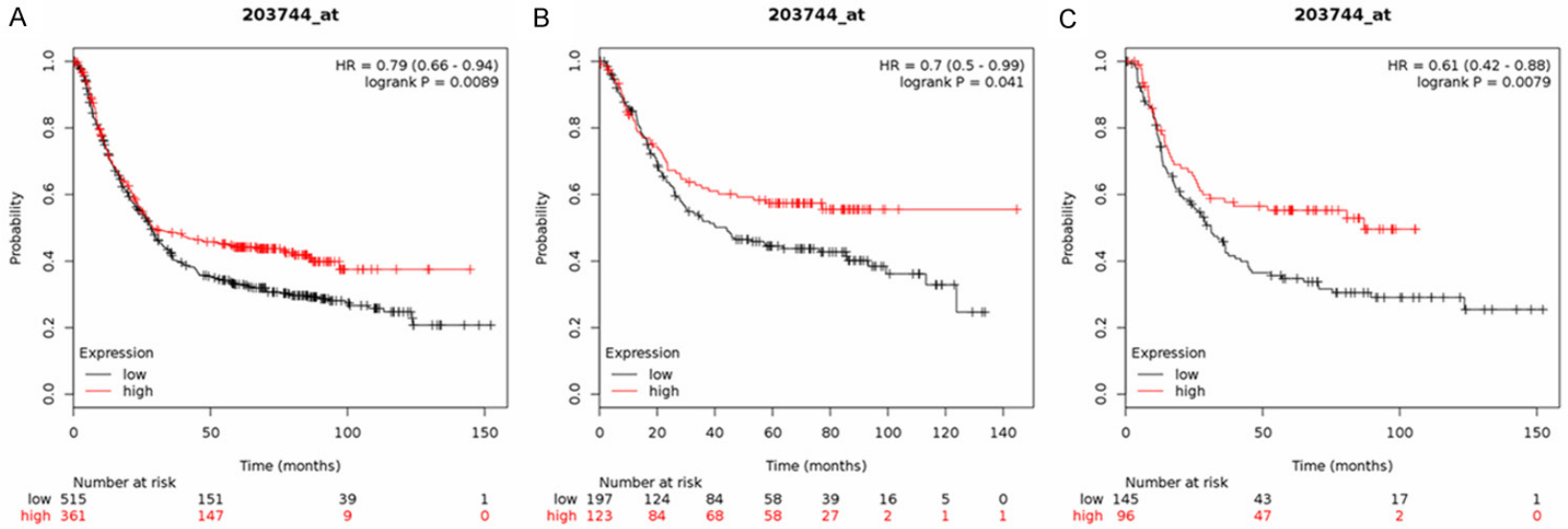

Figure 3. A Kaplan-Meier plotter analysis of the association between the *HMGB3* mRNA levels and overall survival in GC patients. The desired Affymetrix IDs is valid: 203744_at (*HMGB3*). A. Kaplan-Meier survival curves were generated for all GC patients (*n*=876), regardless of the type; B. Kaplan-Meier survival curves were created for the GC patients with the intestinal type (*n*=320); C. Kaplan-Meier survival curves were generated for the GC patients with the diffuse type (*n*=241).

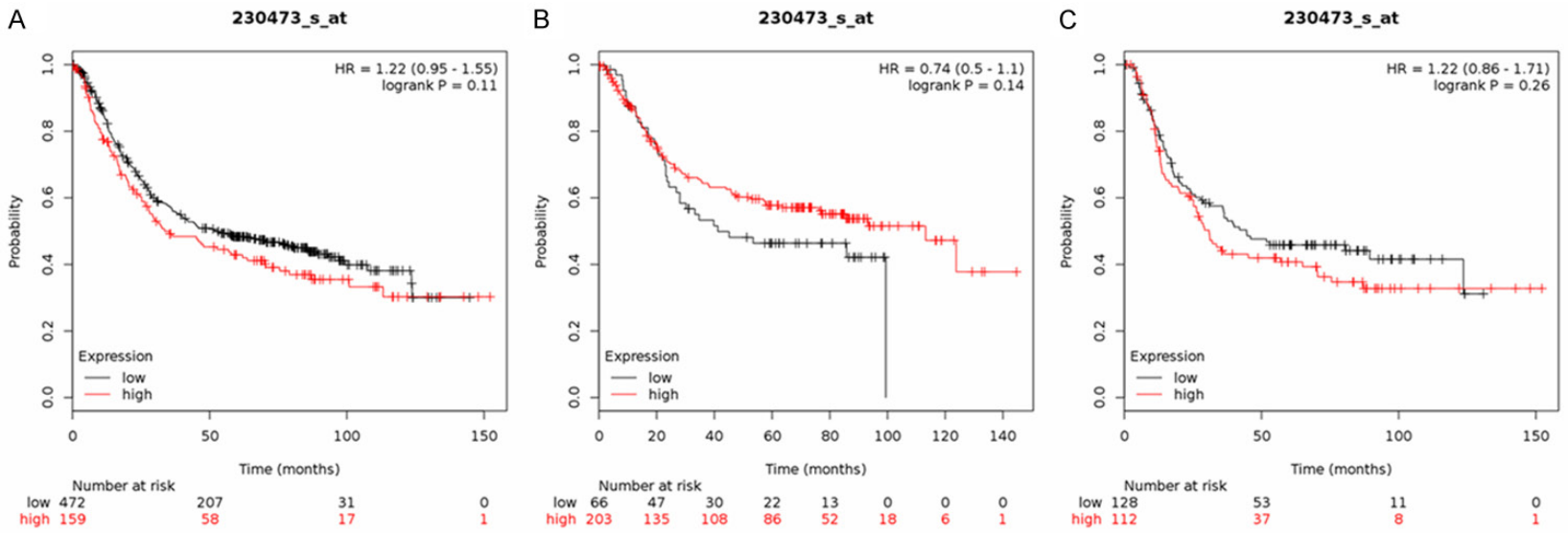

Figure 4. A Kaplan-Meier plotter analysis of the correlation between the *HMGB4* mRNA levels and overall survival in GC patients. The desired Affymetrix ID was valid: 230473_s_at (*HMGB4*). A. Kaplan-Meier survival curves were created for all GC patients (*n*=876), regardless of the type; B. Kaplan-Meier survival curves were created for the GC patients with the intestinal type (*n*=320); C. Kaplan-Meier survival curves were generated for the GC patients with the diffuse type (*n*=241).

Table 1. Correlation analysis of the mRNA expressions of the HMGB family and gender in gastric cancer patients

HMGBs	Gender	Cases	HR 95% CI	*P*-value
HMGB1	Male	545	0.57 (0.45-0.71)	5.4e-07
	Female	236	0.45 (0.31-0.67)	5.5e-05
HMGB2	Male	545	0.49 (0.38-0.63)	1.50e-08
	Female	236	0.44 (0.30-0.65)	2.60e-05
HMGB3	Male	545	0.79 (0.64-0.98)	0.035
	Female	236	0.46 (0.29-0.76)	0.0016
HMGB4	Male	349	0.77 (0.56-1.07)	0.12
	Female	187	0.80 (0.50-1.29)	0.37

and individuals (HR: 0.61 [0.42-0.88], *P*=0.0079; **Figure 3C**) with the diffuse type of GC, respectively. However, the KM survival curve revealed a null association between the HMGB3 mRNA expression and OS in patients with the intestinal type of GC (HR: 0.7 [0.5-0.99], *P*=0.041; **Figure 3B**).

A similar analysis was conducted for HMGB4 using the Affymetrix ID of 230473_s_at. The KM survival curves were plotted for HMGB4 in 631 GC patients (**Figure 4A**), 269 patients with the intestinal type of GC (*n*=269, **Figure 4B**), and 240 patients with the diffuse type of GC (**Figure 4C**). The KM survival curves did not identify any correlation between the HMGB4 mRNA expression and OS in all the GC patients (HR: 1.22 [0.95-1.55], *P*=0.11; **Figure 4A**), the patients with the intestinal type of GC (HR: 0.74 [0.5-1.1], *P*=0.14; **Figure 4B**), or the patients with the diffuse type of GC (HR: 1.22 [0.86-1.71], *P*=0.26; **Figure 4C**).

Correlation analysis of the mRNA expressions of the HMGB family and overall survival by gender, pathological grade, clinical stage, HER2 status, and treatment

Next, a further analysis was performed to examine the correlation between the mRNA expressions of the HMGB family members and the selected clinicopathological features, including gender (**Table 1**), pathological grade (**Table 2**), clinical stage (**Table 3**), the HER2 status (**Table 4**), and the treatment methods (**Table 5**).

As presented in **Table 1**, the higher HMGB1 mRNA expression levels and the higher HMGB2 levels were significantly related to greater OS in both the male and female GC patients. However, the HMGB3 mRNA expressions in the female GC patients were the same. Furthermore, higher HMGB3 mRNA levels were not significantly correlated with OS in the male GC patients. Similarly, no significant difference between males and females was identified in terms of the relationship between the higher HMGB4 mRNA expressions and OS. Interestingly, no correlation was detected between the HMGB family mRNA expressions and the pathological grade (I, II, and III) among the GC patients.

Table 3, shows that higher HMGB1 mRNA expression levels were significantly associated with longer OS in stage I, II, and III GC patients. However, the analysis did not reveal any association with between the HMGB1 mRNA expression and stage IV GC. In addition, the HMGB2 mRNA expression was significantly related to better OS in the stage III GC and stage IV GC patients. It is noteworthy that the higher HMGB3 and HMGB4 mRNA levels were not associated with all the clinical stages (I, II, III, and IV) of GC.

Next, the study subjects were stratified in terms of their HER2 statuses, as seen in **Table 4**. Higher HMGB1, HMGB2, and HMGB3 mRNA expression levels were significantly correlated with favorable OS in the GC patients with a negative HER2 status. However, the HMGB4 mRNA expression did not have any correlation with OS, regardless of the HER2 status.

As shown in **Table 5**, the GC patients were assigned to two subgroups, according to the different treatments they received: the surgical treatment group, or the 5-fluorouracil (5-FU) chemotherapy group. Their HMGB1 and HMGB2 mRNA levels were significantly correlated with the longer survival rate in GC patients who received surgical treatment alone, while the correlation was not observed in the GC patients. In addition, higher HMGB3 mRNA expressions were significantly associated with poor OS in the GC patients who received the 5 FU-based adjuvant chemotherapy. However, no significant association between the HMGB4 mRNA expressions and OS was observed in the patients who underwent surgical treatment or chemotherapy with 5 FU alone.

Discussion

The major findings of this study are summarized as follows: (1) The HMGB family mRNA expressions are significantly correlated with OS

Table 2. Correlation analysis of the mRNA expressions of the HMGB family and the pathological grades in gastric cancer patients

HMGBs	Pathological grades	Cases	HR 95% CI	*P*-value
HMGB1	I	32	0.38 (0.14-1.04)	0.049
	II	67	0.40 (0.19-0.86)	0.015
	III	165	1.37 (0.92-2.04)	0.12
HMGB2	I	32	0.43 (0.17-1.11)	0.073
	II	67	0.69 (0.31-1.54)	0.37
	III	165	1.28 (0.82-1.98)	0.2
HMGB3	I	32	1.70 (0.65-4.41)	0.27
	II	67	1.51 (0.68-3.32)	0.31
	III	165	1.67 (1.05-2.65)	0.029
HMGB4	I	5	0 (0-Inf)	0.046
	II	67	0.57 (0.29-1.09)	0.086
	III	121	1.46 (0.85-2.52)	0.17

Table 3. Correlation analysis of the mRNA expressions of the HMGB family and the clinical stages in gastric cancer patients

HMGBs	Clinical stages	Cases	HR 95% CI	*P*-value
HMGB1	1	67	0.26 (0.10-0.71)	0.0046
	2	140	0.44 (0.23-0.83)	0.0094
	3	305	0.64 (0.48-0.85)	0.0019
	4	148	0.80 (0.55-1.17)	0.25
HMGB2	1	67	0.12 (0.02-0.88)	0.013
	2	140	0.49 (0.25-0.97)	0.035
	3	305	0.49 (0.35-0.70)	5.70e-05
	4	148	0.55 (0.35-0.86)	0.0087
HMGB3	1	67	0.24 (0.07-0.86)	0.018
	2	140	0.64 (0.35-1.20)	0.16
	3	305	0.76 (0.57-1.02)	0.063
	4	148	0.64 (0.42-0.98)	0.04
HMGB4	1	62	3.37 (1.02-13.6)	0.033
	2	135	0.63 (0.33-1.18)	0.14
	3	197	0.66 (0.44-1.00)	0.046
	4	140	1.47 (0.95-2.27)	0.079

in GC patients. (2) There is a significant association between higher HMGB1, HMGB2, or HMGB3 mRNA levels (but not HMGB4 mRNA levels) and better OS in GC patients. (3) A greater mRNA expression of a specific HMGB family member is significantly correlated with the clinical characteristics of GC (e.g. histological classification, pathological grade, clinical stage, HER2 status, and treatment method).

Among the four HMGB family members, HMGB1 is expressed in various cell types and functions as a pro-inflammatory cytokine [18]. A growing body of evidence supports HMGB1's role in cancer progression and metastasis through its promotion of the migration and angiogenesis of malignant cells [10, 19-22]. Several previous studies have suggested that HMGB1 is abnormally elevated in nearly 85% of GC patients and is associated with the advanced stages and poor GC prognoses [23, 24]. Chung *et al.* also found that extracellular HMGB1 is significantly elevated during the development of the epithelial-mesenchymal transition (EMT), which is considered to be a critical process for metastasis in GC [25]. *In vitro* and *in vivo* studies have indicated that HMGB1 depletion results in inhibitory effects on both cell growth and invasion *via* the NF-κB signaling pathway [26]. Song and colleagues reported that the inhibition of HMGB1 prevented the excessive cell proliferation and invasion in GC, and that this holds promise as a novel therapeutic target for GC [27]. However, the findings of some studies were not consistent with the above results. For instance, Akaike *et al.* reported that GC patients with lower levels of HMGB1 had a shorter survival when compared to patients with higher HMGB1 levels [28]. Bao *et al.* found that HMGB1 may not be correlated to the stages, invasiveness, or lymph node metastasis of GC, but a high HMGB1 expression may indicate a good GC prognosis after surgery and chemotherapy [29]. In the present study, a high HMGB1 mRNA expression was significantly related to better OS for all GC patients, and a similar correlation could be found for the intestinal type of GC, but not for the diffuse type of GC.

HMGB2 has been shown to play a key role in osteoarthritis, neuronal degeneration, and aging [30-32]. However, unlike HMGB1, little has been determined about the role of HMGB2 in GC. An *et al.* indicated that HMGB2 expression is significantly higher in GC when compared to the controls [33], and the silencing of HMGB2 reveals the reverse of multidrug resistance in GC. In agreement with these previous

Table 4. Correlation analysis of the mRNA expressions of the HMGB family and the HER2 status in gastric cancer patients

HMGBs	HER2 status	Cases	HR 95% CI	*P*-value
HMGB1	Negative	532	0.52 (0.41-0.66)	3.2e-08
	Positive	344	0.77 (0.57-1.04)	0.091
HMGB2	Negative	532	0.52 (0.41-0.66)	2.40e-08
	Positive	344	0.69 (0.51-0.95)	0.022
HMGB3	Negative	532	0.67 (0.54-0.84)	0.00052
	Positive	344	0.85 (0.60-1.11)	0.2
HMGB4	Negative	429	0.83 (0.63-1.12)	0.22
	Positive	202	1.30 (0.86-1.96)	0.21

Note: HER2, human epidermal growth factor receptor-2.

Table 5. Correlation analysis of the mRNA expressions of the HMGB family and the different treatments in gastric cancer patients

HMGBs	Treatment	Cases	HR 95% CI	*P*-value
HMGB1	Surgery alone	380	0.65 (0.49-0.87)	0.063
	5-FU based Adjuvant	153	0.71 (0.50-1.02)	0.063
HMGB2	Surgery alone	380	0.53 (0.38-0.76)	0.00037
	5-FU based Adjuvant	153	1.37 (0.96-1.94)	0.079
HMGB3	Surgery alone	380	0.73 (0.55-0.98)	0.034
	5-FU based Adjuvant	153	2.83 (1.93-4.14)	3.10e-08
HMGB4	Surgery alone	380	0.75 (0.55-1.02)	0.068
	5-FU based Adjuvant	34	0.44 (0.17-1.16)	0.089

findings, Cui *et al.* reported that higher HMGB2 expressions were found in 198 GC tissues when compared to non-cancerous matched samples [34]. Furthermore, the same study identified a connection between the HMGB2 expression and the clinical parameters, including the association between higher expressions of HMGB2 and larger tumor sizes, a more advanced T stage, and a greater possibility of lymph node metastasis. Notably, it was found that higher HMGB2 expressions were significantly associated with better OS in GC, the intestinal type of GC, and the diffuse type of GC.

HMGB3 represents an X-linked member of the HMG-box subfamily [35]. An increasing number of investigations have revealed that the upregulation of HMGB3 is correlated with the rapid progression as well as a poor prognosis of breast cancer, lung cancer, and GC [29, 36-39]. Tang and colleagues reported that HMGB3 is elevated in GC tissues when compared to peritumoral tissues [38], suggesting a relationship between higher HMGB3 expressions and a poor GC prognosis. The silencing of the HMGB3 gene led to inhibitory effects in the proliferation of GC cells. Gong *et al.* also proposed the role of HMGB3 in the potential regulation modes underlying GC, in which nine transcription factors were found to interact with HMGB3, and they noted that these transcription factors can regulate the proliferation, migration, and invasion of GC cells [40]. After HMGB3 is downregulated, the sensitively of the GC cells to cisplatin, and paclitaxel was found to be enhanced. In the present study, it was found that higher HMGB3 mRNA levels are significantly correlated with better OS for all GC patients, including patients with the diffuse type of GC.

HMGB4 has been recently identified as a member of the HMGB family [41]. To date, studies on HMGB4 in GC remain very limited. Like other members of the HMGB family, HMGB4 might play a role in cancer. Recently, a study conducted by Awuaha *et al.* demonstrated that HMGB4 has a role in sensitizing testicular germ cell tumors to cisplatin chemotherapy [42], and similar results were also found with breast cancer cells when they were complemented with HMGB4. More research is needed on the role of HMGB4 in increasing the sensibility of cisplatin to cancer. In this study, it was observed that the HMGB4 mRNA levels were not correlated with OS for GC patients, GC patients with the diffuse type, and GC patients with the intestinal type.

HER2 has been recognized as a promising molecular target in the treatment of GC [43-45]. HER2 is considered the most effective targeted agent mainly due to ability to improve OS in GC, as shown in two meta-analyses [46-48]. The anti-HER2 antibody, trastuzumab, has been highly recommended as a treatment option for HER2-postive GC patients [49]. It is noteworthy in the study that HER2-negative GC patients had better OS when HMGB1, HMGB2, or HMGB3 was highly expressed, but HMGB4

was not significantly correlated with OS, regardless of the status of HER2 in GC patients.

It may merit attention in this study that higher HMGB1 and HMGB2 mRNA expressions were significantly related to better OS in GC patients undergoing surgical treatment alone. Interestingly, higher HMGB3 mRNA levels were significantly correlated with worsened OS in the GC patients who received 5-FU-based adjuvant therapy.

In summary, the findings of the KM plotter survival analysis demonstrate the prognostic values of the four HMGB family members in GC. Three HMGB members, excluding HMGB4, have been significantly correlated with better OS for all GC patients. These results suggest a potentially novel role of the specific HMGB members (alone or in combination) in the prognosis of GC with different clinical features. Although further studies are needed, these findings may benefit the development of better approaches for the more accurate prediction of GC prognoses. Furthermore, these results may offer potential molecular targets in the development of therapeutic drugs for GC.

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Disclosure of conflict of interest

None.

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