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Prognostic significance and molecular mechanisms of adenosine triphosphate-binding cassette subfamily C members in gastric cancer

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Abstract

Gastric cancer (GC) is one of the major leading causes of tumor-related deaths worldwide. Adenosine triphosphate-binding cassette subfamily C (ABCC) consists of 13 members, ABCC1 to 13, which were examined for their associations with GC.

The online Kaplan–Meier Plotter database was used to determine the prognostic significance of ABCC subfamily members in GC. Stratified analyses were performed using gender, disease stage, degree of tumor differentiation, expression of human epidermal growth factor receptor 2 (HER2), and Lauren classification. Molecular mechanisms were examined using the database for annotation, visualization, and integrated discovery database.

ABCC1, *ABCC3*, *ABCC7*, *ABCC8*, *ABCC9*, and *ABCC10* expression showed prognostic significance in the whole population and in male and female subpopulations (all $P \leq .05$). Furthermore, high expression of most ABCC family members always suggested a poor prognosis, except for *ABCC7* ($P > .05$). Stratified analyses revealed that *ABCC1*, *ABCC3*, *ABCC7*, *ABCC8*, *ABCC9*, and *ABCC10* expression showed prognostic significance for the whole population, as well as male and female populations. *ABCC2* and *ABCC9* were significantly correlated with all disease stages, while *ABCC2* and *ABCC6* were significantly correlated with all Lauren classifications. Expression of *ABCC1*, *ABCC3*, *ABCC5*, *ABCC7*, *ABCC8*, *ABCC9*, and *ABCC10* was significantly correlated with either negative or positive of HER2 status (all $P \leq .05$). Enrichment analysis indicated that these genes were involved in ATPase activity, transmembrane transport, or were ABC transporters (all $P \leq .05$).

ABCC1, *ABCC3*, *ABCC7*, *ABCC8*, *ABCC9*, and *ABCC10* may be potential prognosis biomarkers for GC, acting as ABC transporters and via ATPase activity.

Abbreviations: ABC = ATP-binding cassette, ABCC adenosine triphosphate-binding cassette subfamily C, ATP = adenosine triphosphate, BP = biological process, CC = cellular component, CI = confidence interval, DAVID = database for annotation, visualization and integrated discovery, GC = gastric cancer, GGI = gene–gene interaction, GO = gene ontology, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, KEGG = Kyoto Encyclopedia of Genes and Genomes, MF = molecular function, MRPs = multidrug resistance proteins, OS = overall survival.

Keywords: ABCC family, gastric cancer, Kaplan–Meier plotter, molecular mechanism, prognostic significance

1. Introduction

Accumulating evidence has indicated that gastric cancer (GC) is one of the major leading causes of malignancy-related deaths worldwide.[1] It was estimated that there were approximately 1 million new GC patient cases in 2018 and about half of new cases occurred in China.[2] The relative 5-year overall survival (OS) rate of GC is less than 25% due to disease invasion and metastasis, compared to an OS of more than 90% for patients diagnosed at an early stage of GC.[3–5] Although early diagnosis and treatment of GC, including surgery, targeted therapy, adjuvant therapy, and radio-chemotherapy have greatly improved outcomes, the prognosis of GC patients with advanced stage GC remains poor and unsatisfactory.[1,6] Currently, research has identified several oncogenic and tumor suppressor genes, microRNAs and proteins as potential biomarkers for GC.[7] These biomarkers have been associated with tumorigenesis, tumor progression, and aggressiveness. Nonetheless, these novel biomarkers need further validation in other cohorts. Therefore, identification of new biomarkers for early diagnosis and prognosis prediction for GC is very important.

The adenosine triphosphate (ATP)-binding cassette (ABC) transporters are a superfamily of membrane proteins which play significant roles in transporting various exogenous and endogenous substances across membranes against concentration gradients through ATP hydrolysis.[8] The *ABC* gene family has been divided into 7 subfamilies, the ABCA, ABCB, ABCC, ABCD, ABCE, ABCF, and ABCG subfamilies.[8]

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The ABCC subfamily consists of 13 member genes: *ABCC1*, *ABCC2*, *ABCC3*, *ABCC4*, *ABCC5*, *ABCC6*, *ABCC7* (also known as *CFTR*), *ABCC8*, *ABCC9*, *ABCC10*, *ABCC11*, *ABCC12*, and *ABCC13* (https://www.genenames.org/data/genegroup/#!/group/807).[9] Nine of these transporters are well known as multidrug resistance proteins (MRPs).[10]*ABCC1*, also known as *MRP1*, is responsible for drug and xenobiotic disposition in organisms and for protecting human organs and tissues from cytotoxic assault.[11]*ABCC2*, also known as *MRP2*, plays a pivotal role in biliary elimination of several endogenous substances such as leukotriene C_4 and conjugated bilirubins.[12,13]*ABCC3*, also known as *MRP3*, compensates for *MRP2* deficiency in liver tissue.[14]*ABCC4*, also known as *MRP4*, plays an important role in cellular efflux of cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP) and some secondary messengers.[15] Similar to *MRP4*, *MRP5* (*ABCC5*), is not only a nucleotide organic anion transporter, but also regulates the efflux of substances such as cAMP, cGMP, and several purine analogs.[16]*MRP7* (*ABCC10*) is highly expressed in colon tissue, skin, and testes.[17]*MRP8* (*ABCC11*) was first reported to be highly expressed in breast cancer via a database mining and prediction program.[18]*MRP9* (*ABCC12*) may also play important roles during meiotic prophase and spermatid development in males.[19]

Currently, little is known about the association between GC and ABCC subfamily members. Therefore, we conducted this study to investigate the prognostic significance of 13 ABCC family members in the OS of GC patients.

2. Material and methods

2.1. Data source

We used the online database, Kaplan–Meier plotter (http://kmplot.com/analysis/), to analyze the prognostic significance of mRNA expression of ABCC family members in GC.[20] This database contains transcriptomic data from 1065 patients based on datasets from 3 major medical centers in Berlin, Bethesda, and Melbourne.[20] In the present study, OS was evaluated to determine prognostic significance in a total of 882 GC patients. Differences in OS were analyzed after stratification by gender and status of human epidermal growth factor receptor 2 (HER2) expression (HER2-positive or negative). Subtype analysis was performed based on cancer stage (stage 1, 2, 3, or 4), Lauren classification (intestinal, diffuse, or mixed), and tumor differentiation (poor, moderate, or well-differentiated). Probe numbers used in the study of ABCC1 to 13 were 202804-at, 206155-at, 214979-at, 203196-at, 226363-at, 214033-at, 205043-at, 210245-at, 208561-at, 213485-s-at, 224146-s-at, 1552590-a-at, and 1552582-at, respectively. In addition, low and high expression groups were divided by median mRNA expression.

2.2. Ethics approval

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

2.3. Gene ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of ABCC family members involved in GC

To explore potential GO terms and KEGG pathways, we used the online database for annotation, visualization, and integrated discovery, version 6.8 (DAVID; https://david.ncifcrf.gov/).[21,22] DAVID provides users with a comprehensive set of functional annotations of biological processes (BPs) for lists of genes.

2.4. Gene-gene interaction (GGI), protein-protein interaction (PPI), and GO networks

The GGI network was constructed using the geneMANIA plugin in Cytoscape software.[23,24]*ABCC13* was not recognized in the GGI network and *ABCC7* was recognized as cystic fibrosis transmembrane conductance regulator *(CFTR)*. The PPI network of ABCC members was constructed using the STRING online database (https://string-db.org/).[25] ABCC11 was not recognized in the PPI network. Visualization of GO networks including BP, cellular component (CC), and molecular function (MF) networks were constructed using the BinGO plugin in Cytoscape software.[26]

2.5. Statistical analysis

SPSS version 24.0 (IBM, Armonk, NY) was used for statistical analysis. A P-value $\leq .05$ was considered statistically significant. The 95% confidence interval (CI) and hazard ratio (HR) were used for risk assessment in Cox proportional hazards regression analysis.

3. Results

3.1. The association of ABCC family members with OS

The prognostic value of ABCC family members in GC was determined by their association with OS. *ABCC1* and *ABCC2* showed prognostic differences between the low and high expression groups (both $P < .01$, Fig. 1A and D). In addition, high expression of these genes always indicated a poor prognosis. Prognostic differences were also observed between high and low expression of *ABCC3,* but not for *ABCC4* (*ABCC3*: $P = 3.2E\text{-}14$, *ABCC4*: $P = 0.12$, Fig. 2A and D). Moreover, high expression of *ABCC3* was associated with poor prognosis. *ABCC5* showed a prognostic difference between low and high expression groups, whereas *ABCC6* did not (*ABCC5*: $P = 9.1E\text{-}5$, *ABCC6*: $P = 0.22$, Fig. 3A and D). High expression of *ABCC5* was associated with poor prognosis. *ABCC7* and *ABCC8* also showed prognostic differences (both $P < 0.01$, Fig. 4A and D), but in this case low expression of *ABCC7* and high expression of *ABCC8* indicated poor prognosis. *ABCC9* and *ABCC10* as well as *ABCC11* and *ABCC12* showed prognostic differences, where high expression was consistently associated with poor prognosis (all $P < .01$, Figs. 5 and 6AFigs. 5A and D and 6A and D). Finally, a prognostic difference was observed for *ABCC13* in which high expression was associated with decreased OS ($P = .031$, Fig. 7A).

3.2. 3.2 The association of ABCC family members with OS, stratified by gender

To further explore sex-related differences in the OS of patients expressing *ABCC* genes, OS plots for ABCC family members were depicted by gender. *ABCC1*, *ABCC3*, *ABCC7*, *ABCC8*, *ABCC9*, and *ABCC10* showed prognostic significance in both male and female populations (all $P \leq .05$, Figs. 1B and C, 2B and C, 4B, C, E, and F, 5B, C, E, and F), whereas the association of *ABCC4*, *ABCC11,* and *ABCC12* with OS was not significant (all $P > 0.05$, Figs. 2E, F and 6C, E, F). ABCC5 and ABCC6 showed prognostic significance in males alone (both $P \leq .05$, Fig. 3B and

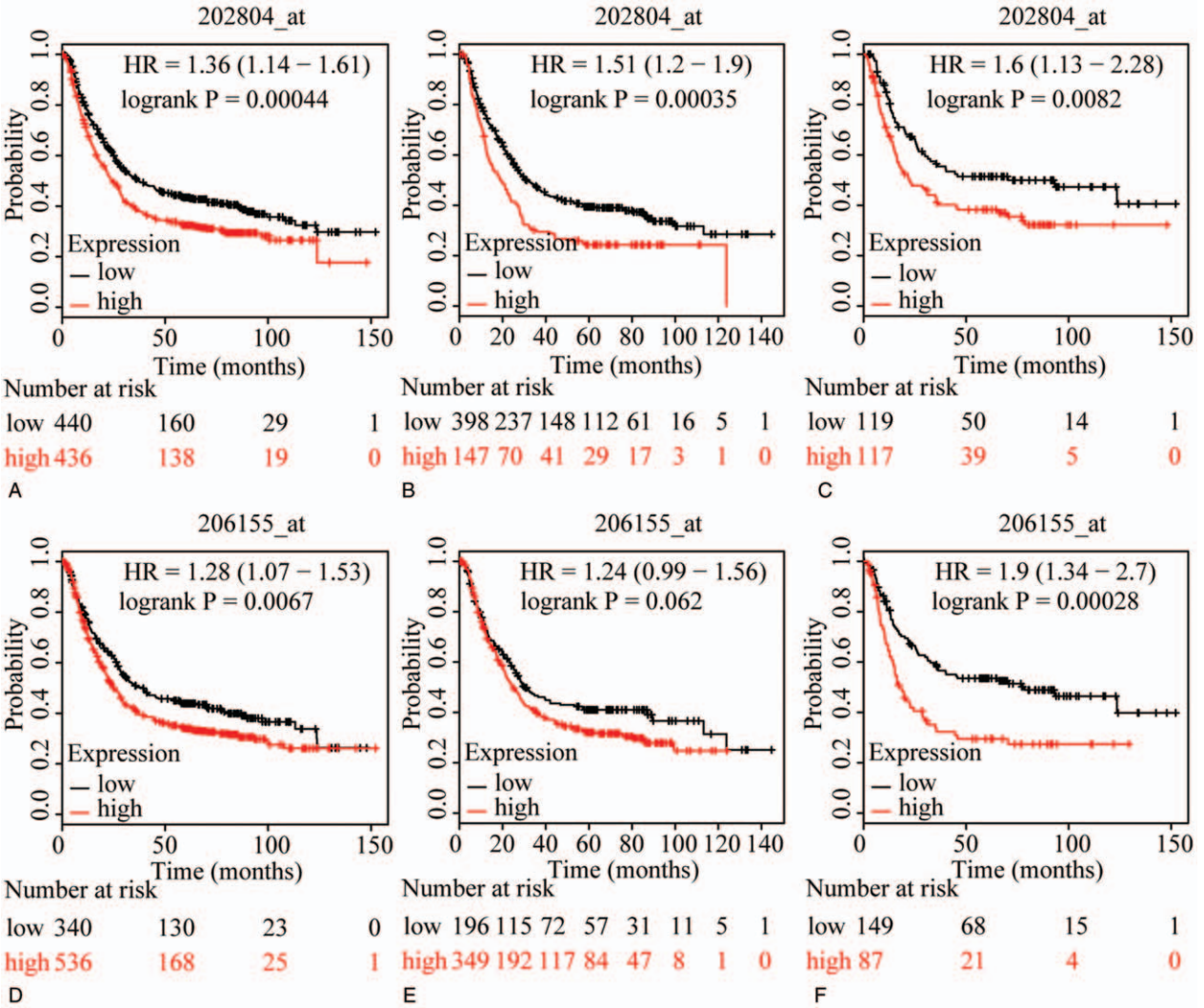

Figure 1. Survival plots of GC patients expressing *ABCC1* and *ABCC2*. (A–C) Survival plots for *ABCC1* (202804_at) in whole, male and female populations, respectively. (D–F) Survival plots for *ABCC2* (206155_at) in whole, male and female populations, respectively. ABCC = adenosine triphosphate-binding cassette subfamily C, GC = gastric cancer.

E), while *ABCC2* and *ABCC13* showed prognostic significance in females only (both $P \leq .05$, Figs. 1F and 7C).

In summary, *ABCC1*, *ABCC3*, *ABCC7*, *ABCC8*, *ABCC9*, and *ABCC10* showed prognostic significance in both the whole population and in segregated male and female populations, whereas the association of *ABCC4* with OS was not significant in any population. However, *ABCC2*, *ABCC5*, *ABCC6*, *ABCC11*, *ABCC12*, and *ABCC13* showed prognostic significance in only some of these populations.

3.3. 3.3 Analysis of GGI, PPI, BP, CC, and MF networks

GGI network analysis indicated that most of the ABCC family members were associated with other ABCA, ABCB, and ABCD family members in shared protein domains. *ABCC3* and *ABCC5* were co-expressed, as were *ABCC8* and *ABCC9*. *ABCC2* was co-expressed with *ABCC1*, *ABCA12*, and *ABCB6* (Supplementary Fig. 1A, http://links.lww.com/MD/D478). In the GGI network, CFTR showed known interactions with ABCC4, ABCC10 and ABCC1 and ABCC8 showed a known interaction with ABCC9. ABCC5 was co-expressed with ABCC1, ABCC2, ABCC3, ABCC6, ABCC8, and ABCC9. ABCC1 was co-expressed with ABCC4, ABCC5, ABCC10, and ABCC12 (Supplementary Fig. 1B, http://links.lww.com/MD/D478).

In the BP network, transmembrane transport, establishment of localization, ion transport, transport, potassium ion transport, and response to drug, among others, were enriched in the network (Supplementary Fig. 2, http://links.lww.com/MD/D479). In the CC network, integral to plasma membrane, intrinsic to membrane, apical part of cell, membrane fraction, cell fraction, cytoplasmic vesicle part, and other functions were enriched in the network (Supplementary Fig. 3, http://links.lww.com/MD/D480). In the MF network, purine nucleotide binding, ATP binding, adenyl ribonucleotide binding, substrate-specific transporter activity, and primary active transmembrane transporter activity were enriched (Supplementary Fig. 4, http://links.lww.com/MD/D481).

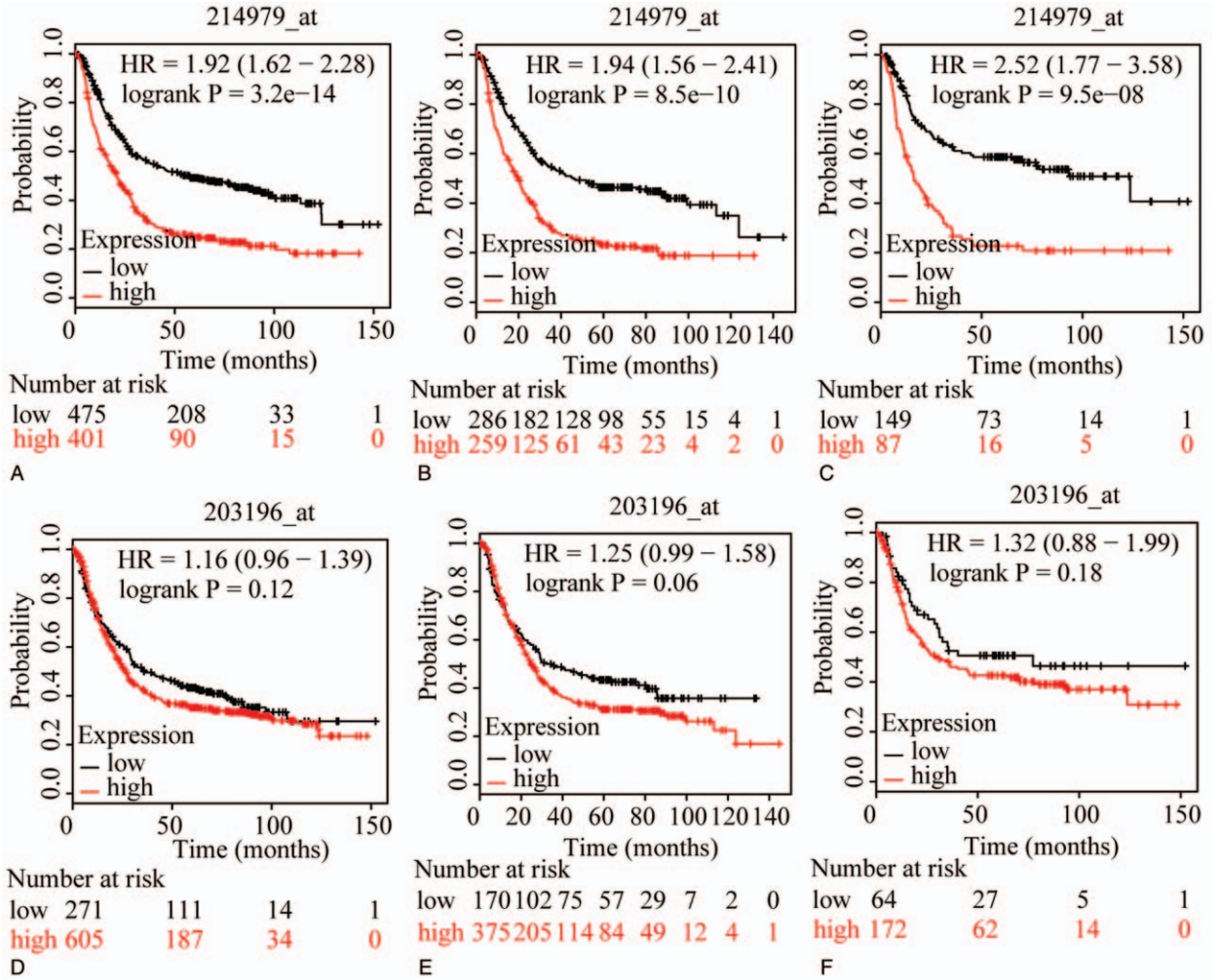

Figure 2. Survival plots of GC patients expressing *ABCC3* and *ABCC4*. (A–C) Survival plots for *ABCC3* (214979_at) in whole, male and female populations, respectively. (D–F) Survival plots for *ABCC4* (203196_at) in whole, male and female populations, respectively. ABCC = adenosine triphosphate-binding cassette subfamily C, GC = gastric cancer.

3.4. Correlation analysis between ABCC family members and disease stage, Lauren classification, tumor differentiation, and HER2 status

Correlation analysis between ABCC family members and cancer stage indicated that all stages were significantly correlated with the expression of ABCC members, *ABCC2* and *ABCC9* (all $P \leq .05$), but none were significantly correlated with any stage. Most of the other family members were significantly correlated with some of the stages (Table 1). Remarkably, a higher stage always indicated a protective role for *ABCC2* and *ABCC9* compared to lower stages, which suggested that low stage may be a poor prognosis predictor. These results were consistently observed for other members as well.

Correlation analysis between ABCC family members and Lauren classification indicated that all of the Lauren classifications were significantly correlated with expression of ABCC members *ABCC2* and *ABCC6* (all $P \leq .05$), whereas none of the Lauren classifications were significantly correlated with *ABCC1* and *ABCC4* (all $P > .05$). Other ABCC family members showed a significant correlation with only some of the Lauren classifications (Table 2). Strangely, HRs were not consistent for *ABCC2* and *ABCC6*: all the HRs were >1 for ABCC2, but HRs were not consistent for the 3 Lauren classifications of ABCC6.

Correlation analysis between ABCC family members and tumor differentiation status indicated that none of the members showed significant correlations with any of the differentiation subtypes. Except for ABCC7 and ABCC8, which did not show any correlation with any of the differentiation subtypes, most ABCC members were correlated with some of the differentiation subtypes (Table 3).

Correlation analysis between ABCC family members and HER2 status indicated that either negative or positive HER2 status was significantly correlated with ABCC members *ABCC1*, *ABCC3*, *ABCC5*, *ABCC7*, *ABCC8*, *ABCC9*, and *ABCC10* (all $P \leq .05$). Moreover, all the HRs were consistent for these members. With the exception of ABCC4 and ABCC11, which were not correlated with any status, other ABCC members were correlated with either positive or negative HER2 status (Table 4).

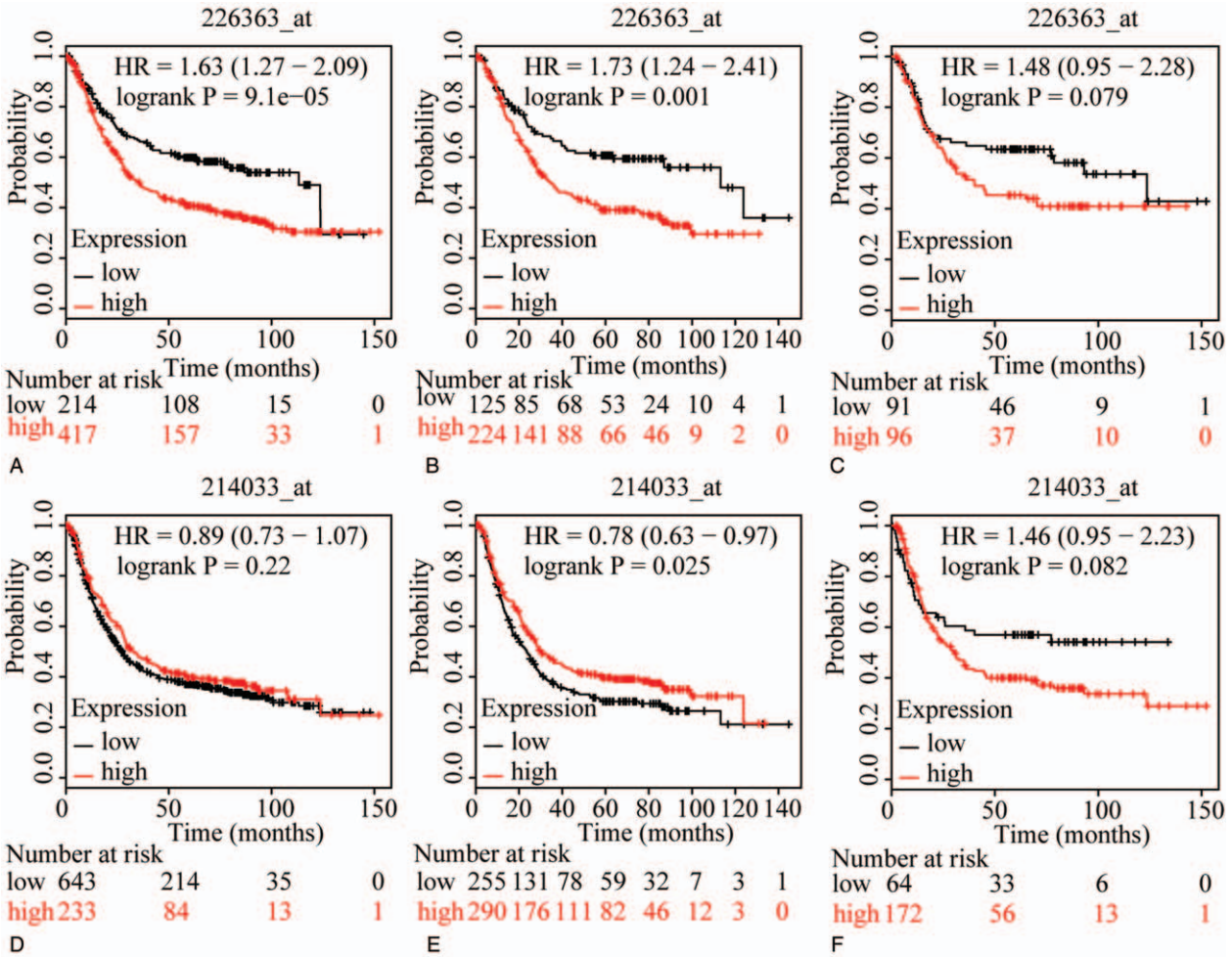

Figure 3. Survival plots of GC patients expressing *ABCC5* and *ABCC6*. (A–C) Survival plots for *ABCC5* (226363_at) in whole, male and female populations, respectively. (D–F) Survival plots for *ABCC6* (214033_at) in whole, male and female populations, respectively. ABCC = adenosine triphosphate-binding cassette subfamily C, GC = gastric cancer.

3.5. Enrichment results of GO terms and KEGG pathways

Enrichment analysis was performed using DAVID. Significant GO terms were enriched for BP, CC and MF, and included ATPase activity, coupled to transmembrane movement of substances, hydrolase activity, acting on acid anhydrides, catalyzing transmembrane movement of substances, transmembrane transport, integral to membrane, intrinsic to membrane, purine ribonucleotide binding, and others (Table 5). These results were consistent with BinGO results (data not shown). The significant KEGG pathway was enriched in ABC transporters (Table 5).

4. Discussion

In the present study, we investigated the association of ABCC family members *ABCC1* to *13* with OS of GC patients. We found that *ABCC1*, *ABCC2*, *ABCC3*, *ABCC5*, *ABCC6*, *ABCC7*, *ABCC8*, *ABCC9*, *ABCC10*, *ABCC11*, *ABCC12*, and *ABCC13* exerted a significant effect on OS. Furthermore, high expression of any of the above genes always suggested a poor prognosis, except for *ABCC7*. Stratified analysis by gender revealed that *ABCC1*, *ABCC3*, *ABCC7*, *ABCC8*, *ABCC9*, and *ABCC10* showed prognostic significance for the whole population as well as male and female subpopulations; in contrast *ABCC4* expression was not significantly different among the above 3 populations. Moreover, *ABCC2*, *ABCC5*, *ABCC6*, *ABCC11*, *ABCC12*, and *ABCC13* showed prognostic significance in some of these populations. Subtype analysis revealed that *ABCC2* and *ABCC9* were significantly correlated with all tumor stages; *ABCC2* and *ABCC6* were significantly correlated with all the Lauren classifications; and *ABCC1*, *ABCC3*, *ABCC5*, *ABCC7*, *ABCC8*, *ABCC9*, and *ABCC10* were significantly correlated with either negative or positive HER2 status. Enrichment analysis indicated that these genes were involved with the GO terms ATPase activity, coupled to transmembrane movement of substances, catalyzing transmembrane movement of substances, transmembrane transport, purine ribonucleotide binding, and others, and were enriched in the KEGG pathway of ABC transporters.

ABC transporters make up a large superfamily of membrane proteins and have been found in many living species from bacteria to human beings.[27] Most of these membrane proteins play a pivotal role in transporting various ATP-dependent substances across lipid membranes, such as sugars, lipids,

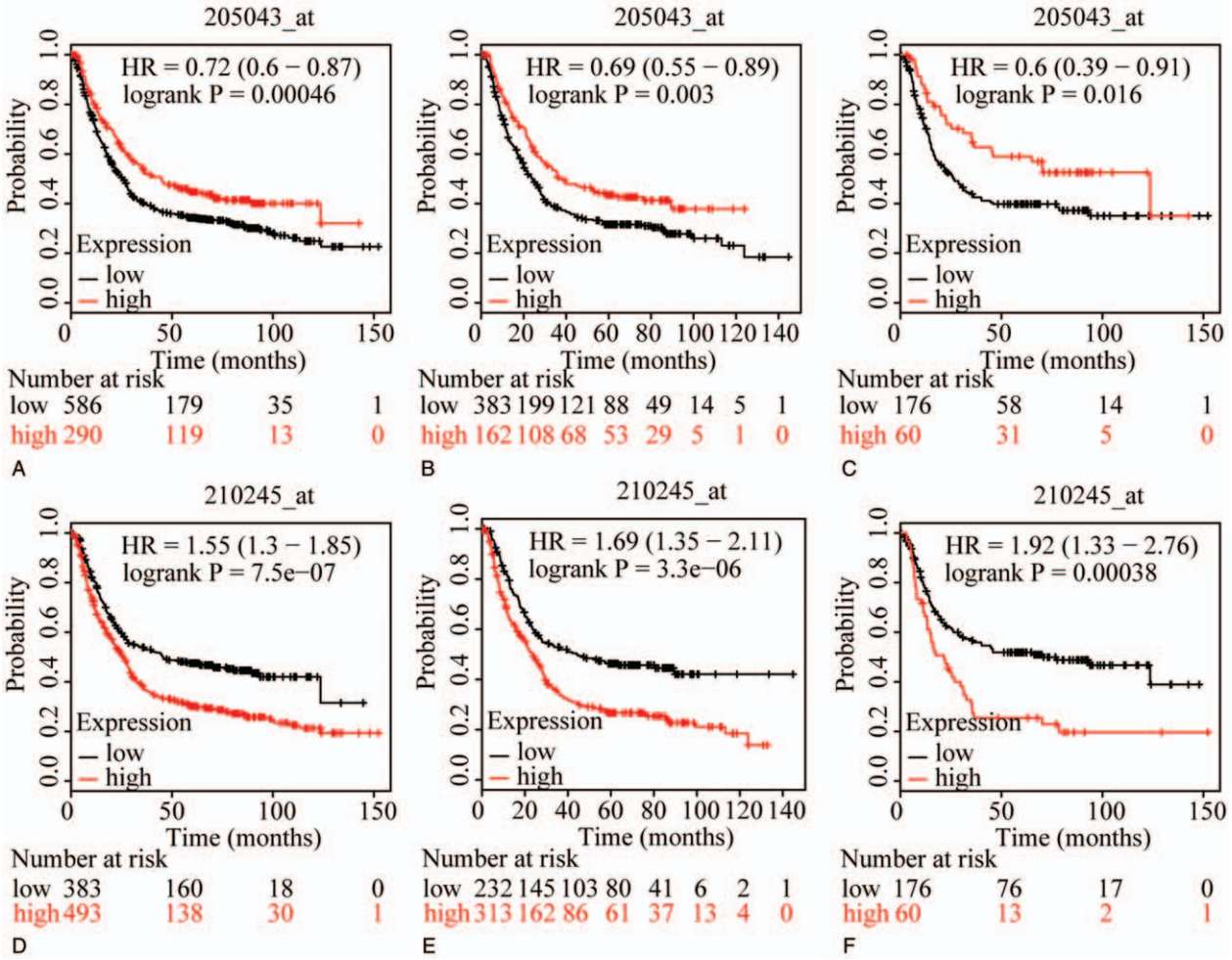

Figure 4. Survival plots of GC patients expressing *ABCC7* and *ABCC8*. (A–C) Survival plots for *ABCC7* (205043_at) in whole, male and female populations, respectively. (D–F) Survival plots for *ABCC8* (210245_at) in whole, male and female populations, respectively. ABCC = adenosine triphosphate-binding cassette subfamily C, GC = gastric cancer.

vitamins, sterols, amino acids, xenobiotics as well as some chemotherapeutic drugs.[28,29] ABC transporters possess highly conserved domains as do all ABC superfamily members, consisting of a highly conserved cytosolic nucleotide-binding domain, while the majority of the superfamily members share less conserved domains.[30] RNA-seq analysis indicated that the *AGAPOO8236* gene, belonging to ABCC subfamily, was greatly upregulated in a deltamenthrin-resistant strain of *Anopheles gambiae*.[31]

ABCC subfamily members are well-known as MRPs and have been reported to be involved in the transportation of many drugs, ions, toxins, and endogenous substances.[28,32,33] *ABCC1* and *ABCC2* protein expression have been detected in mouse and human tissues with chronic pancreatitis.[34] *ABCC1* expression has been associated with chemoresistance of small cell lung cancer by microRNA-7 regulation.[35] A single nucleotide polymorphism of variant alleles of rs12762549 in *ABCC2* has been associated with the risk of anemia.[36] Perego et al demonstrated that *ABCC1* expression was not only associated with tumor grade, but maybe a potential biomarker for aggressiveness of epithelial ovarian cancer, while *ABCC4* may be a poor prognosis predictor in ovarian cancer outcome.[37] Our present study showed results consistent with previous reports that *ABCC1* and *ABCC2* expression were associated with tumor prognosis. In addition, we found that high expression of *ABCC1* and *ABCC2* indicated a poor prognosis for GC.

ABCC3 protein expression has been reported in normal pancreatic tissues and pancreatic adenocarcinoma.[38] Keppler et al suggested that mRNA expression of *ABCC3* was upregulated in pancreatic carcinoma tissues and was associated with tumor stage and grading.[39] *ABCC5* was upregulated in pancreatic carcinoma tissues as well, while *ABCC1*, *ABCC4*, and *ABCG1* were not.[39] These authors further concluded that *ABCC3* and *ABCC5* participated in drug resistance of pancreatic carcinoma and their expression could be used to predict patient response to chemotherapy.[39] *ABCC6* has been found mainly in the basolateral plasma membrane of liver and kidney cells and its mutation has been associated with pseudoxanthoma elasticum, an autosomal recessive disease characterized by progressive ectopic calcification of elastic fibers in vascular, ocular and dermal tissues.[40] Our results indicated that *ABCC3* showed prognostic value in the low and high expression groups, whereas *ABCC4* did not. Moreover, high expression of *ABCC3* was associated with poor prognosis of GC. *ABCC5* also showed

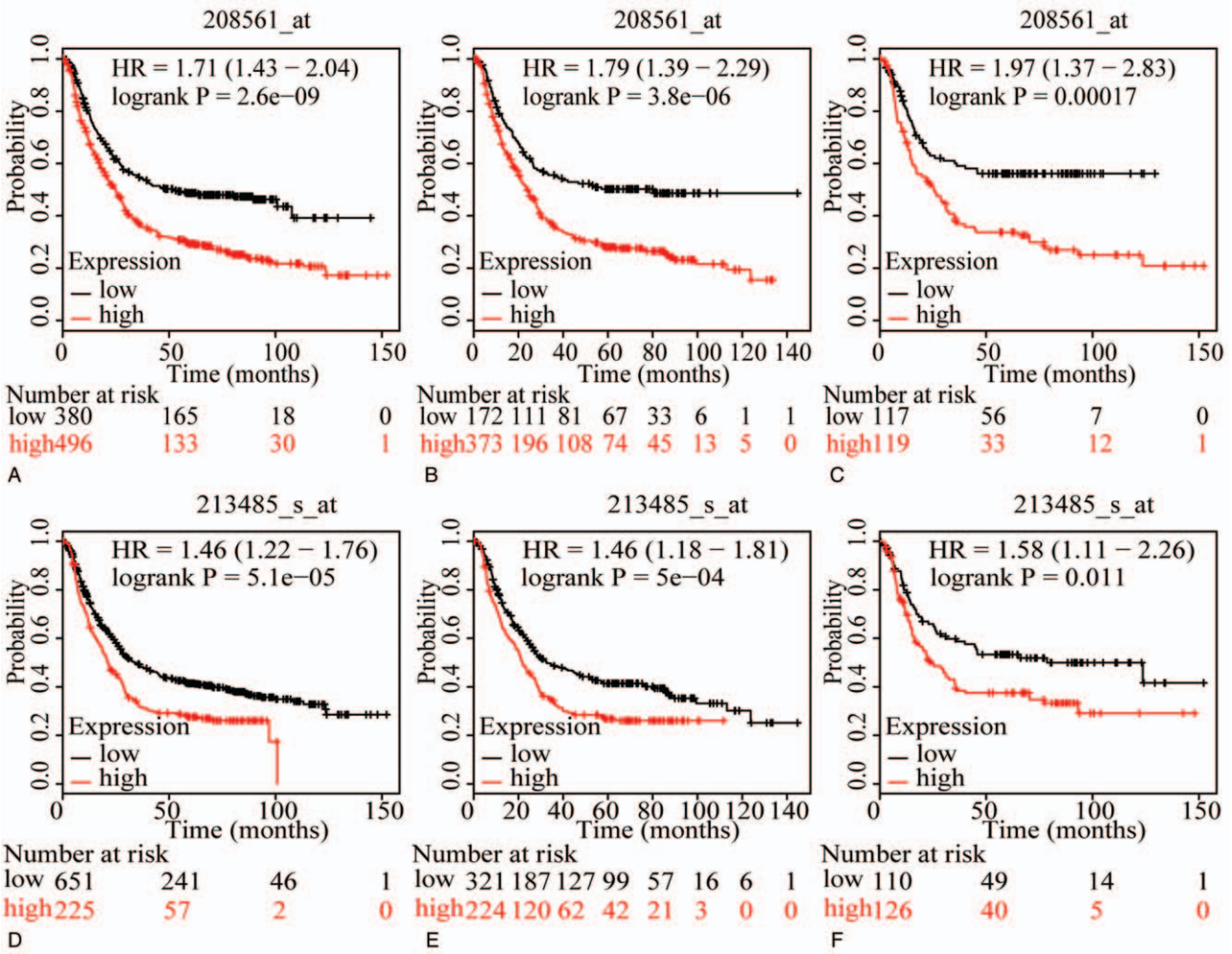

Figure 5. Survival plots of GC patients expressing *ABCC9* and *ABCC10*. (A–C) Survival plots for *ABCC9* (208561_at) in whole, male and female populations, respectively. (D–F) Survival plots for *ABCC10* (203196_at) in whole, male and female populations, respectively. ABCC = adenosine triphosphate-binding cassette subfamily C, GC = gastric cancer.

prognostic value in the low and high expression groups, but *ABCC6* did not. In addition, high expression of *ABCC5* was associated with poor prognosis of GC.

ABCC7, also named *CFTR*, is located on 7q31.2 and has been reported to entail more than 1900 different, heterogeneous mutations in various populations (http://www.genet.sickkids.on.ca/cftr/). *ABCC7* is the main gene contributing to the development of cystic fibrosis.[41,42]*ABCC8* is located on chromosome 11 and its mutation has been related to type 2 diabetes, gestational diabetes and maturity-onset diabetes of the young, which is associated with gene mutations giving rise to abnormalities in pancreatic β cells.[43] Some mutations of *ABCC8* lead to hyperinsulinemia in newborns.[44,45]

Hirota et al reported that *ABCA13*, *ABCB6*, *ABCC1*, and *ABCC3* expression were regulated by cigarette smoke exposure and that *ABCA13*, *ABCC1*, *ABCC2*, and *ABCC9* were differentially expressed in chronic obstructive pulmonary diseases and asthma.[46] Human *ABCC11*, named *MRP8* and located on chromosome 16q12.1, was reported in an investigation of the association between human wet and dry earwax types in geriatric Japanese populations.[47] Dissimilar to other MRP family members, *ABCC11* has some orthologous genes in mammals except for primates.[48,49] Protein expression of ABCC11 has been identified in axons in both central and peripheral nerve system neurons and it may play significant roles in the efflux of neuromodulatory steroids.[50] High expression of *ABCC11* was correlated with poor OS in acute myeloid leukemia patients, which indicates that *ABCC11* may be a predictive biomarker for treatment outcome.[51] Endo et al suggested that high expression of *ABCC11* in breast cancer tissues was significantly associated with poor disease-free survival and aggressive subtypes.[52] Our findings are consistent with these 2 reports indicating that high expression of *ABCC11* is associated poor tumor prognosis.

ABCC12, also known as *MRP9*, has been localized next to *ABCC11* on chromosome 16q12.1, 20 and is oriented in a tail-to-head position, which indicates that *ABCC12* may have originated in a gene duplication event.[48] One of the longest mRNA transcripts of *ABCC12* encodes a protein of 1359 amino acids.[48] Tandemly duplicated on chromosome 16q12 in a region harboring genes for paroxysmal kinesigenic choreoathetosis, *ABCC11* and *ABCC12* are positional candidate biomarkers of this disease.[49] Identified by 2 major transcripts of 4.5 kb and 1.3 kb, *ABCC12* is highly expressed in breast cancer tissue and is

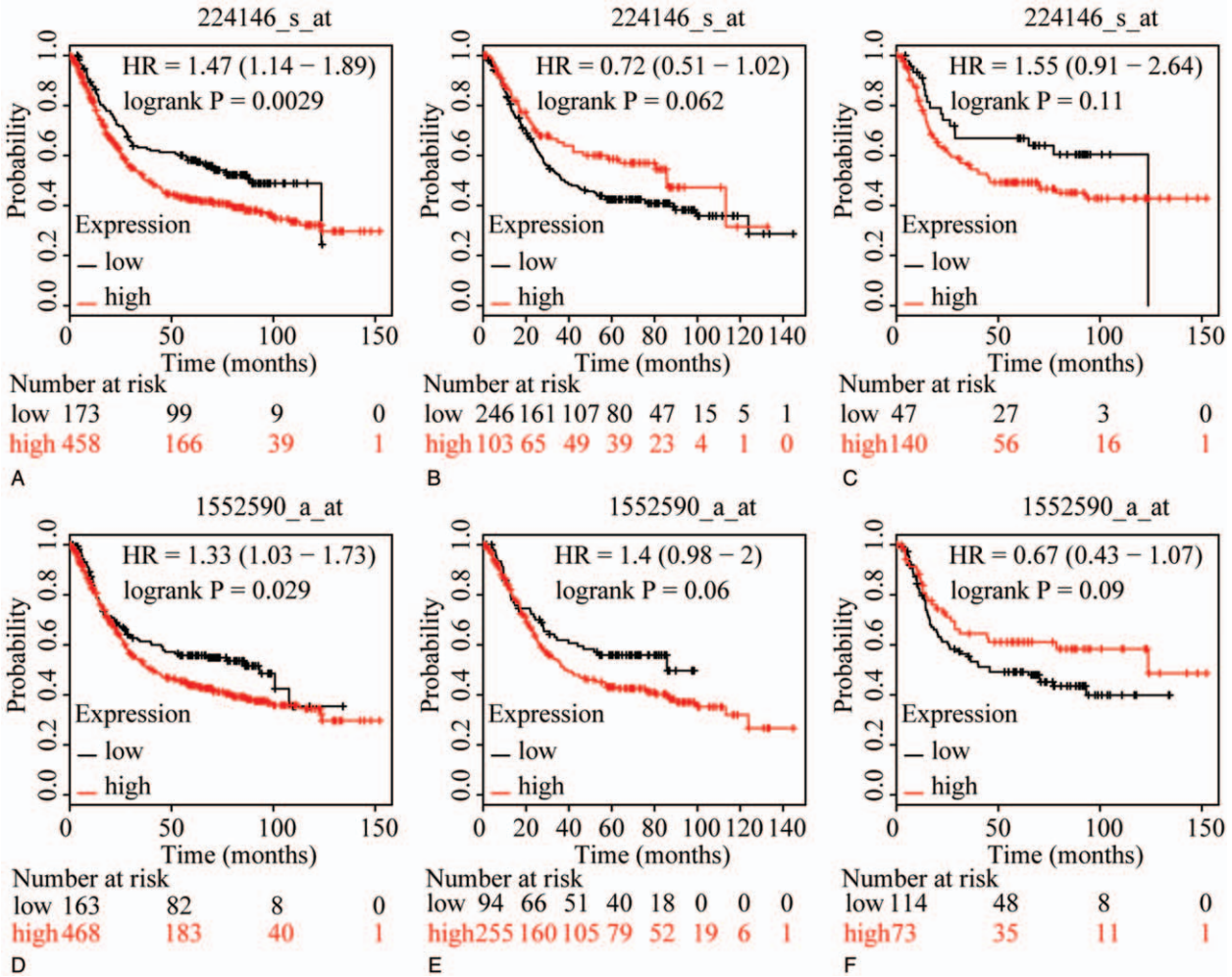

Figure 6. Survival plots of GC patients expressing *ABCC11* and *ABCC12*. (A–C) Survival plots for *ABCC11* (214979_at) in whole, male and female populations, respectively. (D–F) Survival plots for *ABCC12* (213485_at) in whole, male and female populations, respectively. ABCC = adenosine triphosphate-binding cassette subfamily C, GC = gastric cancer.

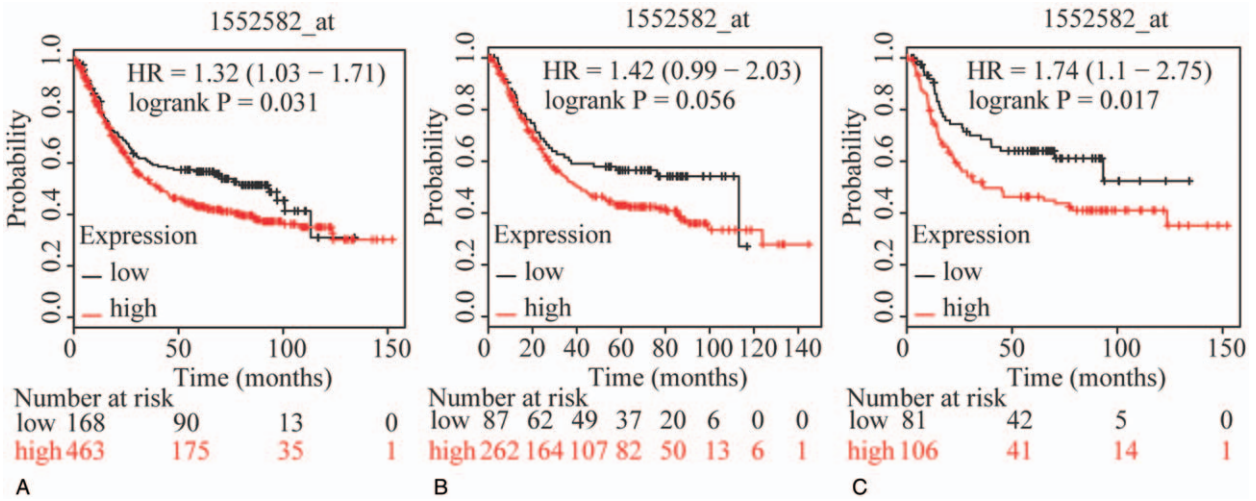

Figure 7. Survival plots of GC patients expressing *ABCC13*, and maps of gene-gene interaction and protein-protein interaction networks. (A–C) Survival plots for *ABCC13* (214979_at) in whole, male and female populations, respectively. ABCC = adenosine triphosphate-binding cassette subfamily C, GC = gastric cancer.

Table 1

Correlation analysis between ABCC family and stage.

Isoenzymes	Stage	Cases	HR	95% CI	*P*-value
ABCC1	1	67	1.17	**1.06–1.31**	**.003**
	2	140	1.42	0.77–2.60	.259
	3	305	1.43	**1.08–1.91**	**.013**
	4	148	0.72	0.48–1.09	.120
ABCC2	1	67	2.93	**1.05–8.20**	**.032**
	2	140	1.97	**1.09–3.58**	**.022**
	3	305	1.48	**1.1–2**	**.010**
	4	148	0.63	**0.41–0.97**	**.033**
ABCC3	1	67	3.28	**1.23–8.78**	**.012**
	2	140	1.56	0.85–2.87	.151
	3	305	1.7	**1.27–2.28**	**<.001**
	4	148	1.36	0.92–2.02	.124
ABCC4	1	67	0.55	0.2–1.49	.233
	2	140	1.69	0.92–3.10	.087
	3	305	0.71	**0.51–0.98**	**.037**
	4	148	0.7	0.47–1.04	.080
ABCC5	1	62	2.05	0.66–6.35	.206
	2	135	1.75	0.92–3.30	.082
	3	197	0.65	**0.43–0.98**	**.037**
	4	140	1.41	0.88–2.27	.156
ABCC6	1	67	3.77	**1.36–10.49**	**.006**
	2	140	2.28	0.96–5.41	.055
	3	305	0.81	0.61–1.09	.167
	4	148	0.58	**0.37–0.92**	**.020**
ABCC7	1	67	2.45	0.84–7.14	.090
	2	140	0.85	0.47–1.55	.592
	3	305	0.64	**0.46–1.89**	**.008**
	4	148	0.61	**0.41–0.90**	**.013**
ABCC8	1	67	7.60	**1.00–57.84**	**.021**
	2	140	1.90	0.88–4.10	.098
	3	305	1.90	**1.40–2.57**	**<.001**
	4	148	1.26	0.84–1.89	.270
ABCC9	1	67	5.65	**1.28–24.97**	**.010**
	2	140	2.22	**1.21–4.08**	**.009**
	3	305	1.86	**1.33–2.6**	**<.001**
	4	148	1.57	**1.07–2.32**	**.021**
ABCC10	1	67	2.39	0.89–6.39	.073
	2	140	1.82	0.84–3.91	.121
	3	305	1.45	**1.09–1.93**	**.011**
	4	148	0.62	**0.42–0.92**	**.018**
ABCC11	1	62	2.50	0.81–7.77	.102
	2	135	1.37	0.73–2.56	.329
	3	197	0.49	**0.30–0.79**	**.003**
	4	140	1.70	**1.08–2.69**	**.021**
ABCC12	1	62	0.17	**0.04–0.76**	**.009**
	2	135	0.66	0.33–1.32	.238
	3	197	1.48	0.94–2.33	.086
	4	140	1.27	0.82–1.96	.275
ABCC13	1	62	2.42	0.74–7.92	.131
	2	135	0.62	0.30–1.31	.208
	3	197	0.73	0.49–1.09	.118
	4	140	1.35	0.90–2.01	.142

Bold fonts indicate statistical *P*-values.
ABCC = ATP-binding cassette subfamily C, CI = confidence interval, HR = hazard ratio.

Table 2

Correlation analysis between ABCC family and Lauren classification.

Isoenzymes	Lauren classification	Cases	HR	95% CI	*P*-value
ABCC1	Instestinal	320	0.83	0.57–1.20	.321
	Diffuse	241	1.37	0.98–1.92	.068
	Mixed	32	2.54	0.92–7.02	.063
ABCC2	Instestinal	320	1.60	**1.13–2.26**	**.008**
	Diffuse	241	1.61	**1.12–2.31**	**.009**
	Mixed	32	3.33	**1.15–9.62**	**.018**
ABCC3	Instestinal	320	2.22	**1.62–3.05**	**<.001**
	Diffuse	241	1.34	0.95–1.88	.094
	Mixed	32	0.64	0.20–2.01	.438
ABCC4	Instestinal	320	**0.77**	0.53–1.14	.192
	Diffuse	241	0.78	0.54–1.13	.185
	Mixed	32	1.85	0.52–6.64	.336
ABCC5	Instestinal	269	1.75	1.08–2.84	.020
	Diffuse	240	1.53	**1.01–2.33**	**.044**
	Mixed	29	5.52	**1.19–25.7**	**.016**
ABCC6	Instestinal	320	0.62	**0.42–0.90**	**.012**
	Diffuse	241	0.66	**0.47–0.93**	**.018**
	Mixed	32	3.17	**1.07–9.37**	**.028**
ABCC7	Instestinal	320	0.50	**0.35–0.73**	**<.001**
	Diffuse	241	0.64	**0.43–0.96**	**.030**
	Mixed	32	2.39	0.82–7.00	.100
ABCC8	Instestinal	320	2.32	**1.67–3.22**	**<.001**
	Diffuse	241	1.40	0.92–2.12	.115
	Mixed	32	2.66	0.84–8.45	.084
ABCC9	Instestinal	320	2.74	**1.98–3.79**	**<.001**
	Diffuse	241	1.78	**1.26–2.52**	**<.001**
	Mixed	32	2.98	0.67–13.36	.134
ABCC10	Instestinal	320	1.72	**1.25–2.37**	**<.001**
	Diffuse	241	0.68	**0.48–0.96**	**.026**
	Mixed	32	251637761.32	0-inf	.063
ABCC11	Instestinal	269	1.36	0.94–1.95	.097
	Diffuse	240	0.65	**0.42–0.99**	**.043**
	Mixed	29	0.39	0.09–1.79	.209
ABCC12	Instestinal	269	1.39	0.93–2.09	.106
	Diffuse	240	0.66	0.43–1.00	.051
	Mixed	29	3.52	**0.95–13.07**	**.046**
ABCC13	Instestinal	269	1.51	0.96–2.39	.074
	Diffuse	240	0.72	0.50–1.04	.081
	Mixed	29	4.00	**1.24–12.89**	**.013**

Bold fonts indicate statistical *P*-values.
ABCC = ATP-binding cassette subfamily C, CI = confidence interval, HR = hazard ratio.

not expressed at detectable levels in normal tissue; thus, it may represent a potential target for immunotherapy of breast cancer.[53]*ABCC13*, found on chromosome 21q11.2 and consisting of 14 exons, spans roughly 70 kb and is highly expressed in human fetal liver.[54] In addition to its similarity to *ABCC2*, the *ABCC13* transcript is made up of 6 exons with a total length of 1.1 kb.[55] The open reading frame of this transcript encodes a polypeptide of 274 amino acids, as compared to other ABC-related transporters with more than 1500 amino acids.[55] Furthermore, the truncated *ABCC13* transcript is specifically expressed in fetal liver, bone marrow, and colon.[55] However, little is known about the association between expression of *ABCC12*, *ABCC13*, and tumors. We are the first to our knowledge to report its prognostic significance in GC patients.

Although we believe we are the first to establish the prognostic significance of ABCC family members in GC, there are still some shortcomings in present study. First, our findings need further validation in other cohorts. Second, multivariate cox regression model should be used for further analysis. Third, experiments in vitro and in vivo should be performed to validate the functions of these prognosis-related genes. In addition, diagnostic significance, including sensitivity and specificity, of ABCC members in GC need to be explored in the future studies. This study also has

Table 3

Correlation analysis between ABCC family and differentiation.

Isoenzymes	Differentiation	Cases	HR	95% CI	*P*-value
ABCC1	Poor	165	1.88	**1.24–2.85**	**.003**
	Moderate	67	1.68	0.84–3.35	.139
	Well	32	2.52	0.74–8.6	.127
ABCC2	Poor	165	1.51	**1.01–2.25**	**.045**
	Moderate	67	1.6	0.82–3.15	.167
	Well	32	2.27	0.67–7.71	.178
ABCC3	Poor	165	1.26	0.81–1.94	.301
	Moderate	67	1.58	0.79–3.16	.190
	Well	32	4.95	**1.14–21.46**	**.018**
ABCC4	Poor	165	1.27	0.85–1.89	.239
	Moderate	67	1.33	0.68–2.60	.395
	Well	32	4.33	**1.67–11.21**	**.001**
ABCC5	Poor	121	1.39	0.84–2.30	.202
	Moderate	67	2.13	**1.08–4.22**	**.026**
	Well	5	2617367754.07	0-inf	.221
ABCC6	Poor	165	0.58	**0.38–0.89**	**.011**
	Moderate	67	0.6	0.32–1.15	.121
	Well	32	0.43	0.14–1.29	.120
ABCC7	Poor	165	1.42	0.90–2.23	.132
	Moderate	67	0.77	0.40–1.48	.436
	Well	32	2.49	0.73–8.49	.131
ABCC8	Poor	165	1.19	0.77–1.85	.421
	Moderate	67	1.82	0.93–3.57	.076
	Well	32	2.36	0.69–8.02	.158
ABCC9	Poor	165	0.71	0.45–1.12	.144
	Moderate	67	2.15	0.94–4.89	.063
	Well	32	3.57	**1.38–9.26**	**.005**
ABCC10	Poor	165	0.78	0.50–1.23	.290
	Moderate	67	2.22	**1.13–4.36**	**.018**
	Well	32	4.84	**1.12–20.96**	**.020**
ABCC11	Poor	121	0.57	**0.34–0.98**	**.039**
	Moderate	67	1.62	0.84–3.12	.142
	Well	5	0	**0-inf**	**.046**
ABCC12	Poor	121	0.69	0.40–1.19	.177
	Moderate	67	2.20	**1.12–4.31**	**.018**
	Well	5	1142066042.6	0-inf	.414
ABCC13	Poor	121	1.78	**1.08–2.93**	**.022**
	Moderate	67	0.44	**0.22–0.88**	**.017**
	Well	5	2617367569.63	0-inf	.221

Bold fonts indicate statistical *P*-values.

ABCC = ATP-binding cassette subfamily C, CI = confidence interval, HR = hazard ratio.

Table 4

Correlation analysis between ABCC family and HER2 status.

Isoenzymes	HER2 status	Cases	HR	95% CI	*P*-value
ABCC1	Negative	532	1.35	**1.06–1.72**	**.016**
	Positive	344	1.50	**1.15–1.96**	**.003**
ABCC2	Negative	532	1.44	**1.15–1.82**	**.002**
	Positive	344	0.85	0.66–1.11	.230
ABCC3	Negative	532	1.99	**1.58–2.50**	**<.001**
	Positive	344	1.98	**1.52–2.56**	**<.001**
ABCC4	Negative	532	0.80	0.61–1.05	.102
	Positive	344	1.33	1.00–1.79	.052
ABCC5	Negative	429	1.71	**1.24–2.36**	**.001**
	Positive	202	1.61	**1.07–2.43**	**.020**
ABCC6	Negative	532	1.28	0.98–1.68	.070
	Positive	344	0.74	**0.56–0.96**	**.025**
ABCC7	Negative	532	0.63	**0.49–0.82**	**<.001**
	Positive	344	0.68	**0.50–0.93**	**.014**
ABCC8	Negative	532	1.70	**1.35–2.13**	**<.001**
	Positive	344	1.33	**1.02–1.73**	**.036**
ABCC9	Negative	532	1.78	**1.41–2.25**	**<.001**
	Positive	344	1.64	**1.24–2.18**	**<.001**
ABCC10	Negative	532	1.29	**1.02–1.64**	**.033**
	Positive	344	1.34	**1.03–1.74**	**.030**
ABCC11	Negative	429	1.32	0.99–1.77	.059
	Positive	202	1.59	0.99–2.54	.052
ABCC12	Negative	429	1.31	0.95–1.80	.098
	Positive	202	0.56	**0.37–0.87**	**.008**
ABCC13	Negative	429	1.42	**1.05–1.91**	**.022**
	Positive	202	0.75	0.51–1.05	.122

Bold fonts indicate statistical *P*-values.

ABCC = ATP-binding cassette subfamily C, CI = confidence interval, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio.

Table 5

Enrichment analysis of gene ontologies and KEGG pathways of ABCC family.

Category	Term	Count	%	*P*-value	FDR
MF	GO:0042626~ATPase activity, coupled to transmembrane movement of substances	13	100	6.58E-26	6.28E-23
MF	GO:0043492~ATPase activity, coupled to movement of substances	13	100	7.38E-26	7.05E-23
MF	GO:0016820~hydrolase activity, acting on acid anhydrides, catalyzing transmembrane movement of substances	13	100	8.28E-26	7.90E-23
MF	GO:0015399~primary active transmembrane transporter activity	13	100	2.72E-25	2.60E-22
MF	GO:0015405~P–P-bond-hydrolysis-driven transmembrane transporter activity	13	100	2.72E-25	2.60E-22
MF	GO:0042623~ATPase activity, coupled	13	100	5.62E-21	5.36E-18
MF	GO:0016887~ATPase activity	13	100	6.92E-20	6.60E-17
BP	GO:0055085~transmembrane transport	13	100	2.74E-17	2.92E-14
MF	GO:0005524~ATP binding	13	100	4.52E-12	4.31E-09
MF	GO:0032559~adenyl ribonucleotide binding	13	100	5.31E-12	5.07E-09
MF	GO:0030554~adenyl nucleotide binding	13	100	9.94E-12	9.49E-09
MF	GO:0001883~purine nucleoside binding	13	100	1.19E-11	1.14E-08
MF	GO:0001882~nucleoside binding	13	100	1.29E-11	1.24E-08
MF	GO:0032553~ribonucleotide binding	13	100	6.20E-11	5.92E-08
MF	GO:0032555~purine ribonucleotide binding	13	100	6.20E-11	5.92E-08
MF	GO:0017076~purine nucleotide binding	13	100	1.05E-10	1.00E-07
MF	GO:0000166~nucleotide binding	13	100	6.97E-10	6.66E-07
MF	GO:0008509~anion transmembrane transporter activity	5	38.46153846	7.28E-06	0.006945089
CC	GO:0016021~integral to membrane	13	100	2.55E-05	0.023698353
CC	GO:0031224~intrinsic to membrane	13	100	3.87E-05	0.03602798
CC	GO:0005624~membrane fraction	7	53.84615385	4.19E-05	0.03899534
MF	GO:0008514~organic anion transmembrane transporter activity	3	23.07692308	5.14E-05	0.049066614
CC	GO:0005626~insoluble fraction	7	53.84615385	5.15E-05	0.047934849
Pathway	hsa02010:ABC transporters	12	92.30769231	5.27E-24	1.66E-21

BP = biological process, CC = cellular component, FDR = false discovery rate, GO = gene ontology, MF = molecular function.

potential bias, including Affymetrix ID choose, cutoff split and subtypes analysis, need to be recognized.

5. Conclusion

Our study has explored the possible relationship of 13 ABCC family members, ABCC1 to 13, with OS of GC patients. Our study found that expression of *ABCC1*, *ABCC2*, *ABCC3*, *ABCC5*, *ABCC6*, *ABCC7*, *ABCC8*, *ABCC9*, *ABCC10*, *ABCC11*, *ABCC12*, and *ABCC13* could predict OS in GC patients. High expression of any of these genes always suggested a poor prognosis except for *ABCC7*. Stratified analysis by gender revealed that *ABCC1*, *ABCC3*, *ABCC7*, *ABCC8*, *ABCC9*, and *ABCC10* showed prognostic significance in the whole population as well as in male and female subpopulations. Subtype analysis revealed that *ABCC2* and *ABCC9* were significantly correlated with all disease stages; *ABCC2* and *ABCC6* were significantly correlated with all of the Lauren classifications; and *ABCC1*, *ABCC3*, *ABCC5*, *ABCC7*, *ABCC8*, *ABCC9*, and *ABCC10* were significantly correlated with both negative and positive HER2 status. Enrichment analysis indicated that these genes were involved in GO terms of ATPase activity, coupled to transmembrane movement of substances, transmembrane transport, purine ribonucleotide binding, and the KEGG pathway of ABC transporters. Nonetheless, although we are the first to report the prognostic significance of ABCC family members in GC, our findings need further validation from other cohorts, and experiments in vitro and in vivo should be used to validate the functions of these prognosis-related genes.

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