Long non-coding RNA polymorphisms on 8q24 are associated with the prognosis of gastric cancer in a Chinese population

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Background. Gastric cancer (GC) remains the third leading cause of cancer death in China. Although genome-wide association studies (GWASs) have identified the association between several single nucleotide polymorphisms (SNPs) on 8q24 and the risk of GC, the role of these SNPs in the prognosis of GC in Chinese populations has not yet been fully evaluated. Therefore, this study was conducted to explore the association between long non-coding RNA (lncRNA) polymorphisms on 8q24 and the prognosis of GC.

Methods. We genotyped 726 surgically resected GC patients to explore the association between eight SNPs in the lncRNAs CCAT1 (rs10087719, rs7816475), PCAT1 (rs1026411), PRNCR1 (rs12682421, rs13252298), and CASC8 (rs1562430, rs4871789, rs6983267) transcribed from the 8q24 locus and the prognosis of GC in a Chinese population.

Results. We found that the patients carrying rs12682421 AA genotypes survived for a shorter time than those with the GG/GA genotype (HR=1.39, 95% CI: 1.09-1.78). Compared with the CC/CT genotype, the TT genotype of rs1562430 was associated with an increased risk of death (HR=1.38, 95% CI: 1.06-1.80). Furthermore, the results also identified the rs1026411 SNP as an independent prognostic factor for poor survival in GC patients. Patients carrying AA/AG variant genotypes had a 36% increased risk of death compared to those carrying the GG genotype (HR=1.36, 95% CI: 1.06-1.74). These findings suggested that the rs12682421, rs1026411 and rs1562430 SNPs may contribute to the survival of GC and be prognostic markers for GC.

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Abstract

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Keywords

Gastric cancer, genetic variation, lncRNA, 8q24, prognosis

Introduction

Gastric cancer (GC) is the fifth most common malignancy and the third leading cause of cancer-related mortality in the world. A total of 1,033,701 new cases of GC were estimated to have occurred in 2018 (Bray et al. 2018). Although the incidence of GC has been declining in the last decades in most regions, it remains a common cancer among many populations in East Asia. Due to a high incidence rate and a large population, more than 40% of GC cases worldwide have occurred in China, according to GLOBOCAN 2012 (Ferlay et al. 2015). In the last decade, the mortality rate of GC has declined conspicuously due to the improved treatment approaches, but the prognosis of GC is still poor in China; the five-year survival rate is 35.9% (Nagini 2012).

GC is a complex and multifactorial malignancy. It has been demonstrated that environmental risk factors, including *Helicobacter Pylori* (*H. pylori*) infection (Lopezsaez et al. 2010), unhealthy diet (Fang et al. 2015), smoking (Fang et al. 2015) and alcohol consumption (Ma et al. 2015b), may be implicated in the pathogenesis of GC. Furthermore, many case-control studies have suggested that host genetic variations play essential roles in the occurrence and progression of GC (Karimi et al. 2014). The results from genome-wide association studies (GWASs) have also identified single nucleotide polymorphisms (SNPs), the most common type of genetic variations in the human genome, in relation to the tumourigenesis of GC (Abnet et al. 2010; Sakamoto et al. 2008; Shi et al. 2011).

GWASs have identified several loci, including 1q22, 5p13.1 and 8q24, that are associated with GC susceptibility, mainly in populations in Asia (Saeki et al. 2013; Sakamoto et al. 2008; Shi et al. 2011; Wadhwa et al. 2013). Particularly, the 8q24 chromosome region has been shown to be involved in several cancer-associated genetic variations that lead to many solid tumours, including prostate, breast, colorectal and gastric cancer (Easton et al. 2007; Gudmundsson et al. 2007; Haiman et al. 2007; Kiemeney et al. 2009; Schumacher et al. 2007; Yeager et al. 2009; Zanke et al. 2007).

In recent years, long non-coding RNAs (lncRNAs) have attracted more attention because several research teams have found many dysregulated lncRNAs in multiple types of tumours (Cao et al. 2013; Ding et al. 2014; Lin et al. 2014; Song et al. 2013). LncRNAs are noncoding transcripts that are more than 200 nucleotides long. Although they were initially regarded as “transcriptional noise”, increasing studies have found that lncRNAs can regulate local or global gene expression through transcriptional, post-transcriptional and epigenetic regulation (Mercer et al. 2009). As lncRNAs play multiple roles in the regulation of gene expression, aberrant lncRNA expression may therefore occur during carcinogenesis and disease development. These

advantages make lncRNAs potential biomarkers for the diagnosis, prognosis and therapy of a variety of cancers, including GC (Zhao et al. 2015b).

The 8q24 chromosome region has been reported to express several lncRNAs in different human and tumours (Xiang et al. 2014). The association between polymorphisms in lncRNAs and the risk of gastric cancer has been studied in several ethnicities (Labrador et al. 2015; Pan et al. 2016; Y et al. 2017). However, there are few studies that have investigated the prognostic value of lncRNA polymorphisms on 8q24 in GC patients. Hence, this study was performed to examine whether variants of lncRNA colon cancer-associated transcript (CCAT1), prostate cancer-associated transcript 1 (PCAT1), prostate cancer non-coding RNA 1 (PRNCR1) and cancer susceptibility candidate 8 (CASC8) genes on chromosome 8q24 are associated with survival in a Chinese population with GC.

Materials & Methods

Study population

Subjects of the study were the newly diagnosed gastric cancer patients recruited from the Department of Gastric and Colorectal Surgery of the First Hospital of Jilin University from 2008 to 2013. A total of 756 patients who underwent tumourectomy without receiving chemotherapy or radiotherapy before surgery were enrolled in this study. The individual characteristics (gender, age) and clinical data (tumour size, histological type, histological grade, lymph metastasis, distant metastasis, depth of invasion, neural invasion and therapy) were collected from the medical records. TNM classification, based on the 2010 seventh edition of the American Joint Committee on Cancer (AJCC) guidelines(Washington 2010), was used to evaluate the clinical stage of the cancer. The evaluation of *H. pylori* infection was performed via a serum immunoglobulin G (IgG) antibody test by an enzyme-linked immunosorbent assay (ELISA) using an *H. pylori*-IgG ELISA kit (Biohit, Helsinki, Finland). Postoperative chemotherapy was identified as an effective therapy for at least 3 cycles.

Ethics Statement

Each patient in this study signed an informed consent form before sample and information collection. This study was approved by the ethics committees of the First Hospital of Jilin University.

Follow-up

The follow-up of the patients was conducted 3 months, 6 months, and 1 year after surgery and every 1 year thereafter until the death of the patient or loss to follow-up. The data from each follow-up visit were collected. Subjects were excluded if they were lost to follow-up at the first phone interview or died due to complications of the surgery during the perioperative period (within 30 days after surgery). The survival time was considered as the duration (i) from the date

of the surgery to the date of death if the GC patient had died or (ii) from the date of the surgery to the date of the last phone interview if the patient was lost to follow-up or to the end of the study if the patient was still alive.

Tagging SNP selection

From whole blood sample of each patient, we extracted genomic DNA using a MagPure Tissue and Blood DNA KF Kit (Magen, Guangzhou, China). The tag SNPs and the well-studied SNPs on 8q24 that were previously reported be associated with gastrointestinal tumours were selected. These SNPs included CCAT1 rs10087719, CCAT1 rs7816475, PCAT1 rs1026411, PRNCR1 rs12682421, PRNCR1 rs13252298, CASC8 rs1562430, CASC8 rs4871789 and CASC8 rs6983267. The SNPinfo (http://snpinfo.niehs.nih.gov/), GVS (http://gvs.gs.washington.edu/GVS147/) and F-SNP (http://compbio.cs.queensu.ca/F-SNP/) databases were used to select tag SNPs. The minor allele frequency (MAF) of all the SNPs was > 0.05 based on the Han Chinese Population.

Genotyping

SNP genotyping was conducted by the MassARRAY technology platform (Sequenom, CA, USA) and was determined by the Bio Miao Biological Technology Co., Ltd. (Beijing). The detection rates for rs10087719, rs7816475, rs1026411, rs12682421, rs13252298, rs1562430, rs4871789 and rs6983267 were 100%, 98%, 99%, 100%, 100%, 100%, 98%, and 94%, respectively.

Transcription factor binding site prediction

Transcription factor binding sites (TFBS) were predicted using the PROMO database (http://alggen.lsi.upc.es/cgi-bin/promo_v3/promo/promoinit.cgi?dirDB=TF_8.3).

Statistical Analysis

Frequency and proportion were used to describe the categorical variables. A goodness of fit χ^2 test was used to test the Hardy-Weinberg equilibrium (HWE) of each SNP. Survival curves of the GC patients based on each SNP were plotted by the Kaplan-Meier method and were compared by log-rank test. The Cox regression model was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) and to evaluate the associations between genotypes of each SNP and overall survival after adjusting for potential confounders (age, gender, *H. pylori*, tumour size, TNM stage, histological type, histological grade, chemotherapy, lymph vascular invasion and neural invasion). All statistical analyses were performed using the SPSS 21.0 software (IBM SPSS, IBM Corp, Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

Results

Characteristics of patients

A total of 756 diagnosed GC patients were enrolled in the study. Fourteen patients died of complications from the surgery during the preoperative period, seven patients were lost to follow-up at the first phone interview and the genotyping of nine patients failed. The remaining 726 patients were included in the study for the subsequent analysis. At the end of the study, 27 patients were lost to follow-up, 357 patients died, and 342 patients were alive (Fig. 1). The duration of follow-up was from 1 month to 109 months, and the median follow-up time was 69.0 months. The characteristics of the 726 patients are shown in Table 1.

Genotype and allele frequencies of the eights SNPs

The genotype frequencies of seven SNPs (rs10087719, rs7816475, rs1026411, rs12682421, rs13252298, rs1562430, rs4871789) in the subjects were in HWE with non-significant χ^2 values (P>0.05). The rs6983267 locus, however, was found to deviate from the HWE (P<0.001). We randomly selected 10% of the samples for repeat genotyping of rs6983267, but the result remained the same. The distributions of the genotype and allele frequencies of the eight SNPs in subjects are shown in **Table 2**. We observed that there was a significant association between the genotypes of rs12682421 and the survival of GC (P=0.03). No associations between genotypes and survival were found for the other SNPs, as shown in **Table 2**.

Multivariate Cox regression analysis of SNPs and gastric cancer survival

A multivariate stepwise Cox regression model was performed to explore the independent prognostic factor for GC. The results showed that tumour size, TNM stage, lymph vascular invasion and chemotherapy were associated with the survival of the patients. The AA genotypes of rs12682421 were associated with a significantly increased risk of death compared with that of the GG/GA genotype (HR=1.39, 95% CI: 1.09-1.78). The TT genotypes of rs1562430 were also associated with increased risk of death compared with that of the CC/CT genotype (HR=1.38, 95% CI: 1.06-1.80). The results also identified rs1026411 SNP as an independent prognostic factor for the poor survival of GC patients; patients carrying AA/AG genotypes had a 36% increased risk of death compared to those carrying the GG genotype (HR=1.36, 95% CI: 1.06-1.74) (**Table 3**). The survival curves of the three SNPs are shown in **Fig. 2**.

Stratified analysis of the genotypes associated with gastric cancer prognosis

Moreover, the associations between the three SNPs (rs12682421, rs1562430, rs1026411) and the survival of the GC patients was evaluated by a stratified analysis of tumour size, TNM stage, lymph vascular invasion and chemotherapy. Compared to patients with the GA/GG genotype of rs12682421, patients with the AA variant genotype had a higher death risk in the subgroup of patients with tumour sizes < 5 cm, an advanced TNM stage, lymph vascular invasion or no postoperative chemotherapy (**Supplementary fig. 1A**). Compared to patients with the CC/CT

genotype, patients carrying TT genotypes of rs1562430 had a higher death risk in the subgroup of patients with tumour sizes ≥ 5 cm, TNM stage III, or lymph vascular invasion and in the subgroup of patients who did not receive postoperative chemotherapy (**Supplementary fig. 1B**). Compared to patient with the GG genotype of rs1026411, patients with the AA/AG variant genotype had a higher death risk in the subgroup of patients with tumour sizes≥ 5 cm or lymph vascular invasion (**Supplementary fig. 1C**).

Discussion

This study aimed to evaluate the possible association between eight lncRNA SNPs on 8q24 and the survival of GC patients in a Chinese population. The multivariate analysis revealed that the AA genotype of rs12682421, the TT genotype of rs1562430 and the AA/AG genotype of rs1026411 were associated with a poor prognosis of GC.

Recent research has suggested that lncRNAs, as oncogenes or tumour suppressor genes, could be involved in the development of cancer and be associated with tumour metastasis and prognosis (Derrien et al. 2012). Given that the majority of the GWAS-identified cancer risk SNPs are located in the noncoding region, the expression and function of lncRNAs are more likely to be impacted by the SNPs (Gao & Wei 2017). Moreover, GWAS have identified 8q24 as a hotspot for cancer-associated SNPs on account of the strength, density and high allele frequency of these SNPs (Sur et al. 2013). Although several studies have revealed that lncRNAs on 8q24, including PRNCR1, CCAT2 and PCAT1, encompass the cancer predisposition SNPs (Eeles et al. 2008; Gaudet et al. 2010; Li et al. 2013; Ling et al. 2013), the prognostic significance of these lncRNAs in GC patients has not yet been fully explored.

PRNCR1, a lncRNA transcribed from 8q24, participates in the carcinogenesis of prostate cancer (PCa) by activating androgen receptor (AR) (Chung et al. 2011); in addition, polymorphisms of the lncRNA PRNCR1 were noted in many cancers, including colorectal cancer (Li et al. 2013), prostate cancer (Chung et al. 2011), and gastric cancer (He et al. 2017). A meta-analysis conducted by Huang et al. (Huang et al. 2018) showed that rs16901946 of PRNCR1, which was in complete linkage disequilibrium (LD) with rs12682421, was associated with an increased risk of gastric cancer in the dominant model. A study performed by He et al. (He et al. 2017) that aimed to assess the GC susceptibility and GC prognostic value of the polymorphisms in PRNCR1, found that rs16901946 G allele carriers (linked with rs12682421 G allele) have an increased risk of GC, but this polymorphism did not exhibit any significant prognostic value for GC. However, in our study, we found that compared with the GA/GG genotype, the PRNCR1 rs12682421 AA genotype was a poor prognostic factor for GC, which is different from the results of the study by He et al. We considered that the reasons for the inconsistent conclusion may be due to the fact that doctor He's study has a smaller sample size (N=494), a shorter follow-up time (the patients were followed for up to 4 years) and fewer events compared with our study.

Rs1562430 is located in the intron of CASC8, a long noncoding RNA (lncRNA), and overlaps with the POU5F1B gene. Previous studies have revealed that the rs1562430 SNP has a strong

association with the risk of breast cancer and colorectal cancer (He et al. 2011; Kim et al. 2012; Zanke et al. 2007). Ma et al. (Ma et al. 2015a) found that there were no associations between the rs1562430 genotype and the survival of GC patients in a Chinese population. However, in the present study, we found that rs1562430 TT was associated with a significantly lower survival rate in GC patients than CC/CT. The study conducted by Ma et al. included patients with TNM stage IV, and the histological type of 42.5% of patients was intestinal. Conversely, our study excluded patients with TNM stage IV, and more than 70% of patients exhibited an intestinal histological type. Moreover, nearly 70% of the patients in our study were infected with *H. pylori.* Therefore, the differences in the pathogenic environment and genetic background of the patients included in the two studies may be the reasons for the inconsistent results.

Existing studies have found that PCAT1 overexpression occurred in PCa, oesophageal squamous cell carcinoma and colorectal cancer (Ge et al. 2013; Prensner et al. 2011). Shi et al. (Shi et al. 2015) identified that ESCC patients with high levels of PCAT1 had poorer survival times than those with low levels of PCAT1. Moreover, recent studies have suggested that a PCAT1 genetic variant may play an essential role in the susceptibility to several cancers (Ren et al. 2017; Zhao et al. 2015a). Yuan et al. (Yuan et al. 2018) found that rs1902432 in PCAT1 was significantly associated with an increased risk of PCa, and Lin et al. (Lin et al. 2017) found that rs710886 of PCAT1 was significantly associated with bladder cancer risk in a Chinese population. As far as we know, no study has been conducted on the role of PCAT1 polymorphisms in the prognosis of GC. In the present study, we found that, compared to GG, rs1026411 AA/AG was associated with a poor prognosis of GC patients (HR: 1.33, 95% CI: 1.03-1.70).

Previous studies have found that the SNPs in lncRNAs have different prognostic values when they occur along with different clinical features (Ma et al. 2015a; Xiong et al. 2017); therefore, we conducted a stratified analysis by tumour size, TNM stage, lymph vascular invasion and chemotherapy. The unfavourable prognostic effects of rs1026411, rs1562430 and rs12682421 were more evident among patients with increased TNM stage and lymph vascular invasion, which indicated that these three SNPs may have higher predictive value in advanced stages of GC. In addition, the results of the stratified analysis showed that rs12682421 and rs1562430 had no predictive value in patients who received chemotherapy but had predictive value in patients who did not receive chemotherapy.

Because lncRNAs could play a crucial role in the regulation of gene expression via transcription and transcription factors often play important roles in tumourigenesis, we used bioinformatics data from the PROMO transcription factor binding site database to predict the possible functions of rs12682421, rs1562430 and rs1026411. We found that the C allele at the rs1562430 locus allowed binding to the glucocorticoid receptor α (GRα), which is a transcription factor that increases genes that participate in cell cycle arrest and apoptosis (JR 2002; Kumar et al. 2004; Yemelyanov et al. 2006). GRα could be bound and activated by glucocorticoids, and previous studies have shown that a higher expression of glucocorticoids receptors has been correlated with a better prognosis in bladder cancer (Ishiguro et al. 2014; Zheng et al. 2012).

Therefore, we considered that the rs1562430 T allele may be associated with a lower GRα expression, which affects the prognosis of the GC patients. Additionally, the A allele at the rs12682421 locus was found to be allowed binding to the GRβ transcription factor, which is a different isoform of GR. GRβ lacks the ligand-binding domain for glucocorticoids (Hinds et al. 2010) and has been indicated to inhibit GRα (Bamberger et al. 1995; D Y et al. 1997; Hinds et al. 2010). GRβ has been demonstrated to be involved in the migration of bladder cancer and brain cancer (Mcbeth et al. 2016; Ying et al. 2013), and some other studies have also reported that GRβ levels are elevated in inflammatory diseases and cancers, leading to increased progression (J C et al. 2001; Jin et al. 2007; Longui et al. 2000; Psarra et al. 2005). Hence, we hypothesize that the poor prognosis of patients with the rs12682421 A allele may be associated with a higher GRβ expression. Moreover, we found that the G allele at the rs1026411 locus facilitated binding to the polyomavirus enhancer activator 3 (PEA3) transcription factor, which belongs to the PEA3 subfamily within the E-twenty-six (ETS) domain transcription factor superfamily (Kandemir et al. 2017). Members of the PEA3 subfamily have been demonstrated in previous studies be associated with a variety of cancers (Cowden-Dahl & Zeineldin 2007; Keld et al. 2010; Launoit et al. 2000; Ping et al. 2010; Shina et al. 2010), but a study conducted by Keld et al. (Keld et al. 2011) showed that PEA3 upregulation in isolation does not predict prognosis in any stage of gastric cancer. The specific roles of GRα, GRβ and PEA3 in gastric cancer should be verified in further studies.

There are several limitations in present study that should be noted. First, although the median follow-up time was 69 months, more than half of the patients survived, and the number of events was insufficient, which may limit the statistical power of our findings. Second, despite the fact that we found associations between three SNPs and overall survival of GC, the mechanisms are still not clear and need to be further elucidated. Third, our study was based on a single group of patients. Hence, other independent replications and multi-centre studies need to be done to explore the role of genetic polymorphisms of lncRNA on 8q24 in the prognosis of GC in different populations.

Conclusions

In summary, the present study revealed that the PRNCR1 rs12682421 AA genotype, the CASC8 rs1562430 TT genotype and the PCAT1 rs1026411 AA/AG genotype could serve as potential markers to predict the unfavourable survival of GC patients in the Chinese population. However, the underlying mechanisms still need to be further studied.

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Competing Interests

The authors declare there are no competing interests.

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Table 1(on next page)

Table 1 Characteristics of the GC patients

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Table 1 Characteristics of the GC patients

Variables		N	%
Age (years)	<60	340	46.8
	≥60	386	53.2
Gender	Male	547	75.3
	Female	179	24.7
Smoking	Yes	281	39.0
	No	440	61.0
Drinking	Yes	198	27.4
	No	524	72.6
Family history	Yes	47	6.5
	No	672	93.5
H. pylori	Positive	438	68.7
	Negative	200	31.3
Tumour Size	<5 cm	420	57.9
	≥5 cm	306	42.1
TNM stage	I	129	17.8
	II	271	37.3
	III	326	44.9
Histological type	Tubular	571	78.6
	Signet-ring cell	68	9.4
	Other	87	12.0
Histological grade	Low-grade	218	30.0
	High-grade	508	70.0
Lymph vascular invasion	Yes	514	70.8
	No	212	29.2
Neural invasion	Yes	399	55.0
	No	327	45.0
Chemotherapy	Yes	314	43.3
	No	412	56.7

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Table 2(on next page)

Table 2 Distributions of the genotypes of the gastric cancer patients

MST: median survival time, months. *Mean survival time was provided when MST could not be calculated

Table 2 Distributions of the genotypes of the gastric cancer patients

Gene	Genotypes		Patients, N	Death, N (%)	MST	Log rank *P*
CCAT1	rs10087719	AA	495	250(50.50)	64.89	0.73
		AG	209	99(47.37)	75.70	
		GG	20	8(40.00)	54.67*	
CCAT1	rs7816475	GG	572	280(48.95)	70.04	0.65
		AG	134	69(51.49)	56.38	
		AA	6	2(33.33)	55.99*	
PCAT1	rs1026411	GG	257	120(46.69)	75.20	0.32
		AG	353	181(51.27)	60.85	
		AA	111	53(47.75)	63.07*	
PRNCR1	rs12682421	AA	443	230(51.92)	58.51	0.03
		GA	248	106(42.74)	68.84*	
		GG	33	21(63.64)	37.78	
PRNCR1	rs13252298	AA	330	158(47.88)	70.05	0.75
		AG	315	157(49.84)	69.29	
		GG	79	42(53.16)	55.39	
CASC8	rs1562430	TT	505	257(50.89)	64.30	0.17
		CT	199	93(46.73)	79.05	
		CC	19	6(31.58)	75.20	
CASC8	rs4871789	GG	251	129(51.39)	64.89	0.64
		AG	344	165(47.97)	73.50	
		AA	119	58(48.74)	67.35	
CASC8	rs6983267	TT	172	89(51.74)	65.68	0.59
		GT	416	195(46.88)	79.05	
		GG	95	48(50.53)	67.35	

MST: median survival time, months. *Mean survival time was provided when MST could not be calculated

Table 3(on next page)

Table 3 Stepwise Cox regression analysis of gastric cancer survival

Age, gender, *H. pylori*, tumour size, TNM stage, histological type, histological grade, chemotherapy, lymph vascular invasion, neural invasion and eight SNPs polymorphism were used as variables in the regression model.

Table 3 Stepwise Cox regression analysis of gastric cancer survival

Genotypes		*P*	Adjusted HR (95% CI)
Tumour size		0.005	1.42(1.11-1.81)
Lymph vascular invasion		<0.001	2.09(1.45-3.02)
TNM stage			
	II vs I	0.007	2.25(1.24-4.07)
	III vs I	<0.001	6.83(3.77-12.36)
Chemotherapy		0.007	0.72(0.56-0.91)
rs12682421 (AA vs GA+GG)		0.009	1.39(1.09-1.78)
rs1562430 (TT vs CC+CT)		0.016	1.38(1.06-1.80)
rs1026411 (AA+AG vs GG)		0.017	1.36(1.06-1.74)

Age, gender, *H. pylori*, tumour size, TNM stage, histological type, histological grade, chemotherapy, lymph vascular invasion, neural invasion and eight SNPs polymorphism were used as variables in the regression model.

Figure 1

Figure 1. Flow chart of the enrolled subjects

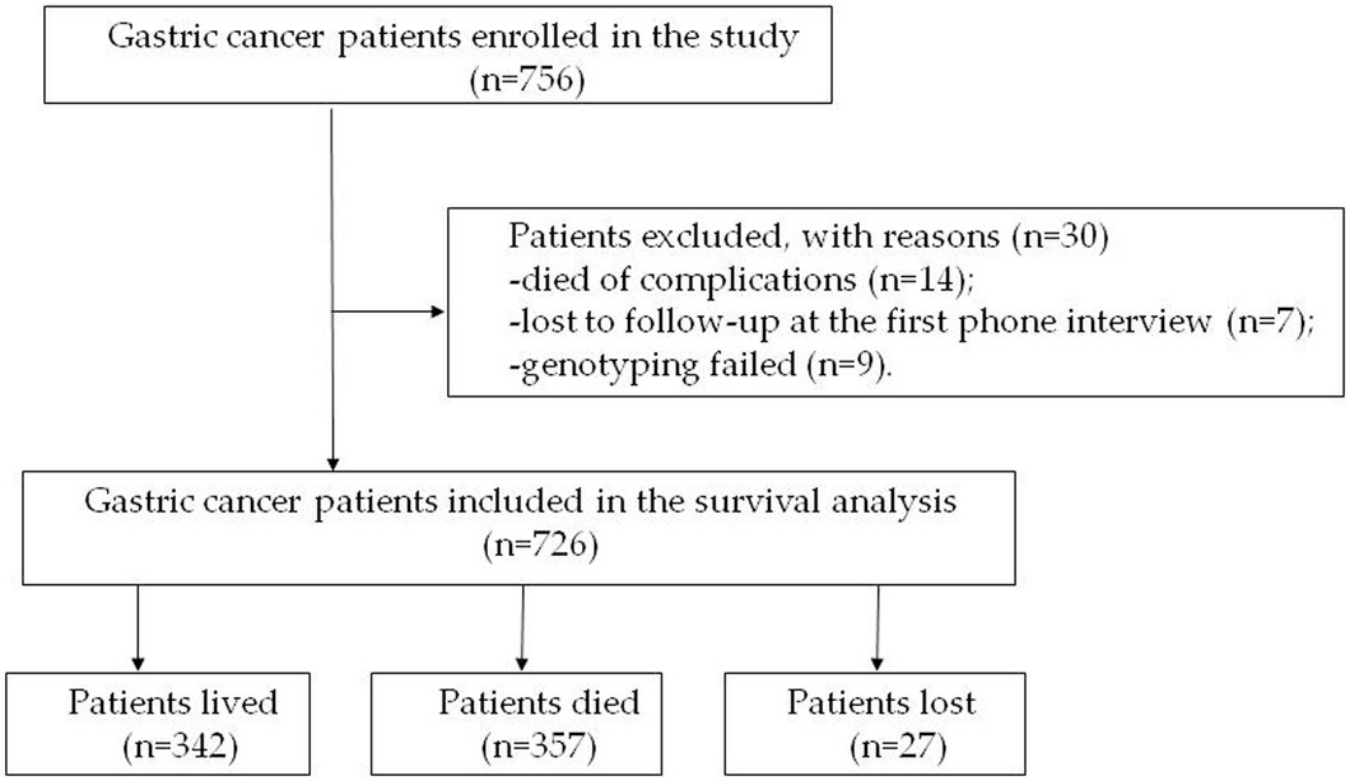

Figure 2

Figure 2. Association of genotypes with overall survival in gastric cancer patients.

A. Plot for rs12682421 using the dominant model (GG/GA vs. AA); B. Plot for rs1562430 using the dominant model (CC/CT vs. TT); C. Plot for rs1026411 using the dominant model (AA/AG vs.GG).