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ORIGINAL ARTICLE

Case Control Study

Investigation of high-mobility group box 1 variants with lymph node status and colorectal cancer risk

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Abstract

BACKGROUND

Accumulating studies indicated that maintain nuclei homeostasis was deemed to the protective factors for the occurrence of cancer. Thus, high-mobility group box 1 (HMGB1) might influence the risk and poorer prognoses of colorectal cancer (CRC).

AIM

This study was designed to investigate whether HMGB1 polymorphisms influence the risk and lymph node metastasis (LNM) of CRC.

METHODS

Firstly, we designed an investigation with 1003 CRC patients and 1303 cancer-free controls to observe whether HMGB1 rs1412125 T > C and rs1045411 C > T SNPs could influence the risk of cancer. Subsequently, we carried out a correlation-analysis to assess whether these SNPs could alter the risk of LNM.

RESULTS
The current investigation suggested a relationship of HMGB1 rs1412125 SNP with the increased susceptibility of CRC. In a subgroup analysis, our findings suggested that this SNP could enhance an occurrence of CRC in ≥ 61 years, non-drinker and body mass index < 24 kg/m^2 subgroups. However, we found that there was null association between HMGB1 rs1412125 SNP and LNM, even in different CRC region. These observations were confirmed by calculating the power value (more than 0.8). The association of HMGB1 rs1045411 C > T SNP with CRC risk and LNM was not found in any compare.

CONCLUSION
This study highlights a possible association between HMGB1 rs1412125 polymorphism and the increased risk of CRC. In the future, more studies should be conducted to explore HMGB1 rs1412125 polymorphism in relation to CRC development.

Key Words: High-mobility group box 1; Colorectal cancer; Polymorphism; Immune; Lymph nodes metastasis

Core Tip: To our knowledge, this study highlights a possible association between high-mobility group box 1 (HMGB1) rs1412125 polymorphism and the increased risk of colorectal cancer (CRC). In the future, more studies should be conducted to explore HMGB1 rs1412125 polymorphism in relation to CRC development.

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INTRODUCTION

In China, colorectal cancer (CRC) was one of the most common digestive tract malignancies, with 376300 new CRC patients and 191000 CRC related deaths happened in 2015[1]. CRC was considered as a complex disease, which involved in the interactions of individuals' genetic parts with many environmental factors. A number of gene loci were found to be correlated with the occurrence and development of CRC[2,3]. According to previous investigations, immune and inflammation might play important roles in the risk and progress of cancer[4-6]. Maintaining homeostasis of nuclei and normal immune were deemed to the protective factors for many malignancies[7,8].

Immune was implicated in a variety of physiological roles and pathological processes, involving in the pathogenesis of autoimmune disease, infectious disease and cancer[9-12]. As a case in point, the incidence of cervical cancer has been reduced after using the human papillomavirus vaccine[13]. High-mobility group box 1 (HMGB1) is a nonhistone DNA-binding protein with high conservation. HMGB1 consists of three domains: (1) A box of DNA-binding domain; (2) B box of DNA-binding domain; and (3) A C terminal with negative charge. In most cells, it can be found in nuclei. It was reported that HMGB1 acted as a DNA chaperone, which could maintain homeostasis of nuclei[14]. As well, HMGB1 was considered as a danger-associated molecular pattern molecule, which played a vital role in inducing inflammation[15-17]. Thus, HMGB1 played a vital role in the occurrence of cancer[18-20]. Of late, HMGB1 was considered as an angiogenesis-related gene. Kusume *et al*[21] reported that HMGB1 secreted by CRC tissue inhibited dendritic cells (DCs) and reduced the ability of anti-cancer immune. HMGB1 expression in CRC patients was associated with poorer prognoses for overall survival[22].

In the past five years, the relationship of HMGB1 rs1412125 T > C single nucleotide polymorphism (SNP) with the susceptibility of cancer has been explored[20,23-29]. However, the observations were conflicting rather than conclusive. Two meta-analysis have been conducted to clarify the potential association of HMGB1 rs1412125 T > C SNP with the risk of overall cancer. These meta-analyses have observed null association. The aim of this investigation was to address the possible relationship between HMGB1 rs1412125 T > C SNP and the risk of CRC more precisely.

A case-control study revealed that rs1045411 C allele in promoter region of *HMGB1* gene was significantly correlated with the early pathologic T stage and pathologic N1 stage of prostate cancer[23]. Another investigation also found that lung cancer (LC) patients with chemotherapy carring HMGB1 rs1045411 C allele had a better overall survival[30]. Additionally, Hu *et al*[31] also found that the HMGB1 rs1045411 C allele reduced the risks of LC. However, a recent study reported that rs1045411 T allele might decrease the risk of urothelial cell carcinoma[20]. Lin *et al*[26] also found an association between rs1045411 T allele and a decrease the risk of oral squamous cell carcinoma. Off late, a meta-analysis suggested that HMGB1 rs1045411 C > T SNP might increase the occurrence of overall cancer[32]. Wang *et al*[28] reported that no significant difference were detected between HMGB1 rs1045411 C > T polymorphism and the risk of CRC. Thus, the association between HMGB1 rs1045411 C > T variant and CRC risk should be further studied.

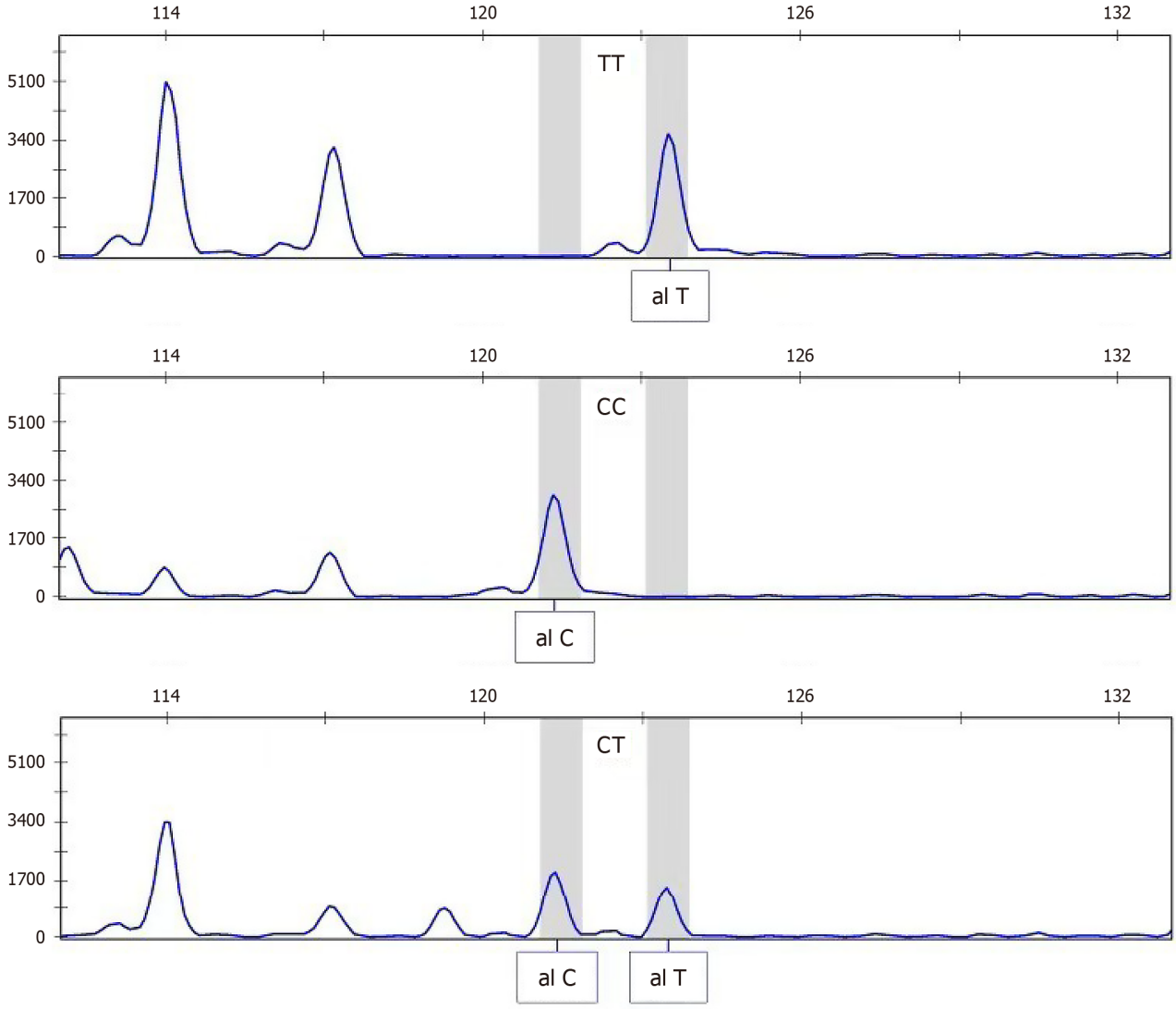

Figure 1 The different genotype of rs1412125.

First, we designed a case-control study to explore whether HMGB1 rs1412125 T > C and rs1045411 C > T SNPs could influence the risk of cancer. Subsequently, we conducted an analysis to assess whether HMGB1 rs1412125 T > C and rs1045411 C > T SNPs could affect the risk of lymph nodes metastasis (LNM).

MATERIALS AND METHODS

Study subjects

In this study, 1003 CRC and 1303 cancer-free controls were recruited from the Fujian Medical University Union Medical College (Fujian Province, China) and Nanjing Medical University Zhenjiang Clinical College (Jiangsu Province, China) between October 2014 and August 2017. All participants were local Chinese Han populations. CRC cases were confirmed *via* histological diagnosis. The controls were individuals without a history of cancer frequency-matched to CRC patients with regarding to sex and age (± 5 years) the same time period. When an interview conducted, a pre-structured questionnaire was used. Then, the data was obtained. Each subject signed an informed consent. Fujian Medical University Ethics Review Committee approved the present study (No. KT2018-003-01).

DNA extraction and genotyping

The genomic DNA was obtained by using DNA isolation kit (Promega, Madison, WI, United States). Before polymerase chain reaction (PCR) testing, it was kept at -80 °C. We used Nanodrop ND-1000 UV to check the quality of DNA. The concentrations and pure of these DNA sample were eligible for PCR test. A custom-by-design 48-Plex SNPscan Kit (Genesky Biotechnologies Inc., Shanghai, China) was used to analyze the genotypes of HMGB1 rs1412125 T > C and rs1045411 C > T SNPs[33]. To carry out a control for genotype test, 92 samples were selected randomly. Using the same PCR method, two authors conducted the genotype test without knowing the status of participants. The findings of original genotype test were not changed. Figure 1 and Figure 2 presented the genotypes of HMGB1 rs1412125 T > C and

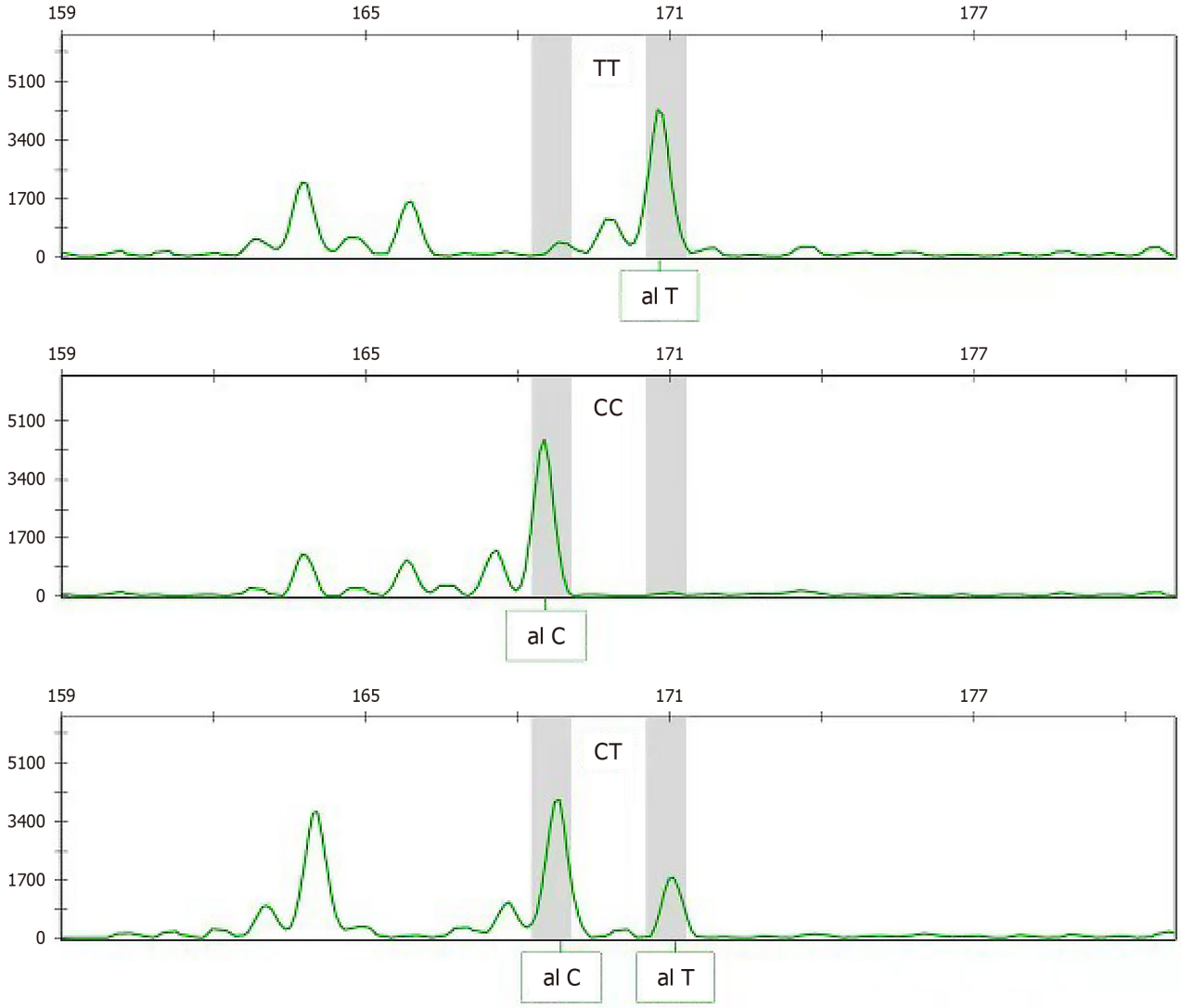

Figure 2 The different genotype of rs1045411.

rs1045411 C > T, respectively.

Statistical analysis

The continuous variable was conducted by *t*-test and expressed as means ± SD. We used SAS 9.4 software for Windows (SAS Institute, Cary, North Carolina) to assess an association of HMGB1 rs1412125 T > C and rs1045411 C > T SNPs with the risk of CRC. Odds ratios (ORs) and 95% confidence intervals (CIs) were harnessed to assess the strength of association between HMGB1 SNPs and CRC susceptibility[34]. *P* value of Hardy-Weinberg equilibrium (HWE) test was performed by online software (https://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The power value was also calculated by using a power and sample size program.

RESULTS

Study characteristics

In this study, 1003 cases with CRC and 1303 cancer-free subjects were recruited (Table 1). The mean age of the case group was 61.10 years. The SD of age was 12.17 years. The mean age and SD of the control group were 61.40 ± 9.61 years. In case group, we included 620 males and 383 females. While in control group, 801 males and 502 females were recruited. In these two groups, the terms of sex and age were full-matched ($P \geq 0.05$). However, the items of drinking, smoking, and body mass index (BMI) were not matched ($P < 0.05$). These detailed data were summarized in our previous study[35].

Variant distribution of HMGB1 rs1412125 T > C and rs1045411 C > T SNPs met HWE in control group ($P > 0.05$). Table 2 lists the SNP information for HMGB1 rs1412125 T > C and rs1045411 C > T loci. The successful ratio of analyzing the genotype was more than 95%.

Table 1 Distribution of selected risk factors and demographic variables in colorectal cancer cases and controls

Variable	Cases (*n* = 1003)		Controls (*n* = 1303)		*P* value[1]
	n	%	*n*	%	
Age (years)	61.10 ± 12.17		61.40 ± 9.61		0.496
Age (years)					0.605
< 61	451	44.97	600	46.05	
≥ 61	552	55.03	703	53.95	
Sex					0.867
Male	620	61.81	801	61.47	
Female	383	38.19	502	38.53	
Smoking status					0.002[a]
Never	744	74.18	1038	79.66	
Ever	259	25.82	265	20.34	
Alcohol use					< 0.001[a]
Never	829	82.65	1167	89.56	
Ever	174	17.35	136	10.44	
BMI (kg/m^2)					
< 24	670	66.80	688	52.80	< 0.001[a]
≥ 24	333	33.20	615	47.20	
Site of tumor					
Colon cancer	431	42.97			
Rectum cancer	572	57.03			

[a]$P < 0.05$.
[1]Two-sided χ^2 test and Student *t*-test.
BMI: Body mass index.

Table 2 Data for high-mobility group box 1 rs1412125 T > C and rs1045411 C > T nucleotide polymorphisms

Genotyped SNPs	Chromosome	Chr Pos (NCBI build 37)	Region	MAF for Chinese in database	MAF in our controls (*n* = 1303)	*P* value for HWE test in our controls	Genotyping method	Genotyping value (%)
HMGB1 rs1412125 T > C	13	31041595	5'flanking	0.24	0.24	0.064	SNPscan	98.87
HMGB1 rs1045411 C > T	13	31033232	3'UTR	0.20	0.20	0.862	SNPscan	98.87

SNPs: Single nucleotide polymorphisms; MAF: Minor allele frequency; HWE: Hardy-Weinberg equilibrium; 3'UTR: 3'untranslated region; HMGB1: High-mobility group box 1.

Association of HMGB1 rs1412125 T > C and rs1045411C > T SNPs with CRC risk

Supplementary Table 1 summarizes raw data. Table 3 lists the number of allele and genotype for HMGB1 rs1412125 T > C and rs1045411 C > T SNPs. In overall comparison, findings of the current study showed that the HMGB1 rs1412125 T > C genotype frequencies were different among CRC patients and controls. An increased frequency of HMGB1 rs1412125 C allele related genotype was identified in CRC group. Compared to HMGB1 rs1412125 TT, subjects with HMGB1 rs1412125 CC genotype, had an increased 76% risk to CRC occurrence ($P = 0.002$). Additionally, in relation to HMGB1 rs1412125 TT, HMGB1 rs1412125 TC/CC was a risk factor for CRC occurrence ($P = 0.029$). Compared to HMGB1 rs1412125 TT/TC, subjects with HMGB1 rs1412125 CC genotype had an increased 67% risk to CRC occurrence ($P = 0.003$). When risk factors were adjusted, an increased risk of CRC occurrence was also recognized ($P = 0.002$, 0.032 and 0.005, respectively). However, the association of HMGB1 rs1045411 C > T SNP with CRC occurrence was not found in overall compare (Table 3).

Table 3 Logistic regression analyses of associations between high-mobility group box 1 rs1412125 T > C polymorphisms and colorectal cancer risk

Genotype	Cases (*n* = 1003)		Controls (*n* = 1303)		Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)[1]	*P* value
	n	%	*n*	%				
HMGB1 rs1412125 T > C								
TT	506	51.63	731	56.23	1.00		1.00	
TC	395	40.31	504	38.77	1.13 (0.95-1.35)	0.161	1.14 (0.95-1.35)	0.160
CC	79	8.06	65	5.00	1.76 (1.24-2.49)	0.002	1.74 (1.22-2.47)	0.002
TC + CC	474	48.37	569	43.77	1.20 (1.02-1.42)	0.029	1.20 (1.02-1.43)	0.032
TT + TC	901	91.94	1235	95.00	1.00		1.00	
CC	79	8.06	65	5.00	1.67 (1.19-2.34)	0.003	1.64 (1.17-2.32)	0.005
C allele	553	28.21	634	24.38				
HMGB1 rs1045411 C > T								
CC	627	63.98	823	63.31	1.00		1.00	
CT	307	31.33	424	32.62	0.95 (0.79-1.14)	0.579	0.94 (0.78-1.13)	0.495
TT	46	4.69	53	4.08	1.14 (0.76-1.71)	0.532	1.10 (0.72-1.66)	0.664
CT + TT	353	36.02	477	36.69	0.97 (0.82-1.15)	0.742	0.96 (0.80-1.14)	0.615
CC + CT	934	95.31	1247	95.92	1.00		1.00	
TT	46	4.69	53	4.08	1.16 (0.77-1.74)	0.475	1.12 (0.74-1.69)	0.589
T allele	399	20.36	530	20.38				

[1]Adjusted for age, sex, body mass index, smoking and drinking status.
OR: Odds ratio; CI: Confidence interval; HMGB1: High-mobility group box 1.

Association of HMGB1 rs1412125 T > C and rs1045411 C > T SNPs with CRC risk in a stratified analysis

We conducted the stratification analyses to determine a potential relationship between HMGB1 rs1412125 and the risk of CRC. Table 4 summarized the results of those analyses (homozygote model: Female subgroup: Adjusted $P = 0.043$; Male subgroup: Adjusted $P = 0.015$; ≥ 61 years subgroup: Adjusted $P = 0.003$; BMI < 24 kg/m^2 subgroup: Adjusted $P = 0.006$; Never drinking subgroup: Adjusted $P = 0.002$ and never smoking subgroup: Adjusted $P = 0.007$; Recessive model: Male subgroup: Adjusted $P = 0.027$; ≥ 61 subgroup: Adjusted $P = 0.004$; Never smoking subgroup: Adjusted $P = 0.012$; Never drinking subgroup: Adjusted $P = 0.004$ and BMI < 24 kg/m^2 subgroup: Adjusted $P = 0.008$).

In this study, we also conducted the stratification analyses to assess the relationship of HMGB1 rs1412125 T > C variant with susceptibility of different CRC subtype. We identified that HMGB1 rs1412125 T > C SNP increased the occurrence of CRC even in different CRC region.

In this study, the relationship of HMGB1 rs1045411 C > T SNP with CRC risk was not found in any subgroup analysis (Table 5 and Table 6).

Relationship between HMGB1 rs1412125 T > C and rs1045411 C > T SNPs and LNM

In the current investigation, a total of 1003 CRC cases were recruited to evaluate a correlation between HMGB1 rs1412125 T > C SNP and LNM. After reviewed the medical history of patients, 518 CRC cases were diagnosed with LNM. Table 7 lists the distribution of HMGB1 rs1412125 T > C genotypes. There was null relationship of rs1412125 T > C variant with LNM. Additionally, we did not find any association of rs1412125 T > C with LNM even in different CRC subtype (Table 8).

In the present investigation, the relationship of rs1045411 C > T with LNM was found neither in overall compare nor in different subgroup analysis (Table 7 and Table 8).

Power of the current investigation

The Type I error probability for a two sided test was used the following criterion: A = 0.05. For HMGB1 rs1412125 T > C SNP, the power value was 0.890 in CC *vs* TT and 0.842 in CC *vs* TC/TT among overall comparison, 0.809 in CC *vs* TT among BMI < 24 kg/m^2 subgroup, 0.864 in CC *vs* TT and 0.824 in CC *vs* TC/TT among non-drinker subgroup and 0.889 in CC *vs* TT and 0.872 in CC *vs* TC/TT among ≥ 61 years subgroup. The power value of other overall and subgroup comparisons was less than 0.8 (data not shown). These results indicated that HMGB1 rs1412125 T > C SNP could be a risk factor of CRC occurrence in non-drinker, ≥ 61 years and BMI < 24 kg/m^2 subgroups and overall comparison.

Table 4 Stratified analyses between high-mobility group box 1 rs1412125 T > C and colorectal cancer risk by sex, age, body mass index, smoking status and alcohol consumption

Variable	HMGB1 rs1412125 T > C (case/control)[1]			Adjusted OR (95% CI); *P* value[2]			
	TT	TC	CC	Additive model	Homozygote model	Dominant model	Recessive model
Sex							
Male	317/461	240/301	47/37	1.16 (0.93-1.45); 0.198	1.77 (1.12-2.81); 0.015	1.23 (0.99-1.53); 0.063	1.67 (1.06-2.62); 0.027
Female	189/270	155/203	32/28	1.11 (0.83-1.47); 0.494	1.77 (1.02-3.08); 0.043	1.18 (0.90-1.56); 0.230	1.69 (0.99-2.90); 0.055
Age							
< 61	199/299	172/213	28/28	1.19 (0.92-1.55); 0.189	1.44 (0.85-2.44); 0.181	1.22 (0.95-1.57); 0.120	1.33 (0.79-2.22); 0.284
≥ 61	307/432	223/291	51/37	1.09 (0.86-1.39); 0.487	2.05 (1.27-3.31); 0.003	1.19 (0.95-1.50); 0.130	1.98 (1.24-3.16); 0.004
Smoking status							
Never	371/573	297/409	60/53	1.11 (0.91-1.36); 0.306	1.73 (1.16-2.57); 0.007	1.18 (0.97-1.43); 0.090	1.65 (1.12-2.43); 0.012
Ever	135/158	98/95	19/12	1.21 (0.83-1.75); 0.320	1.76 (0.82-3.80); 0.148	1.27 (0.89-1.81); 0.185	1.64 (0.77-3.48); 0.201
Alcohol consumption							
Never	416/650	327/457	67/57	1.11 (0.92-1.34); 0.285	1.80 (1.23-2.62); 0.002	1.19 (0.99-1.42); 0.067	1.72 (1.19-2.48); 0.004
Ever	90/81	68/47	12/8	1.29 (0.79-2.09); 0.310	1.37 (0.53-3.55); 0.522	1.30 (0.82-2.06); 0.271	1.24 (0.49-3.14); 0.657
BMI (kg/m^2)							
< 24	338/379	262/273	56/34	1.10 (0.88-1.38); 0.397	1.90 (1.21-3.00); 0.006	1.19 (0.96-1.48); 0.114	1.82 (1.17-2.84); 0.008
≥ 24	168/352	133/231	23/31	1.21 (0.91-1.60); 0.196	1.58 (0.89-2.81); 0.122	1.25 (0.95-1.64); 0.111	1.46 (0.83-2.56); 0.192

[1]The genotyping was successful in 980 (97.71%) cases, and 1300 (99.77%) controls for HMGB1 rs1412125 T > C.
[2]Adjusted for age, sex, body mass index, smoking status and alcohol consumption (besides stratified factors accordingly) in a logistic regression model.
OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; HMGB1: High-mobility group box 1.

DISCUSSION

HMGB1 is a member of angiogenesis-associated genes. Of late, it was identified that HMGB1 might correlate with CRC development[36-38]. In CRC patients, it was regarded as a potent cytokine of pro-angiogenesis which led to vascular endothelial growth factor (VEGF) secretion. In addition, VEGF was considered as a vital regulating role for CRC occurrence and progress. Thus, the consequential correlation suggested that HMGB1 could promote the angiogenesis process of CRC[39]. *Via* the HMGB1/receptor of advanced glycation endproducts/nuclear factor-kappa B (NF-κB) pathway, HMGB1 could also facilitate the cellular proliferation and metastasis of cancer[40,41]. A number of evidences indicated an important affect of individuals' genetic factors in assessing the possible susceptibility for the occurrence and development of cancer. Thus, we explored an association of rs1412125 T > C and rs1045411 C > T variants with CRC risk in a larger sample sizes study. To our knowledge, this case-control study firstly confirmed that HMGB1 rs1412125 T > C SNP could increase the risk of CRC in China.

Rs1412125 T > C was a common SNP in 5'-flanking of *HMGB1* gene, which was a functional region for regulation. A previous study suggested that the HMGB1 rs1412125 T > C SNP could influence the efficacy of platinum-based treatment in patients with LC[42]. Recently, a case-control study focused on a relationship of HMGB1 rs1412125 T > C with the CRC occurrence[28]. However, due to the limited sample sizes, the association of HMGB1 rs1412125 T > C SNP with the risk of CRC was unconfirmed. Li *et al*[43] conducted a pooled-analysis to identify a potential association of HMGB1 rs1412125 T > C SNP with the risk to cancer development. In the meta-analysis mentioned above, nine case-control studies with 4865 cancer cases and 4639 controls were involved for analysis. Although the association of HMGB1 rs1412125 T > C SNP with the risk to cancer development was unconfirmed. This meta-analysis suggested that HMGB1 rs1412125 T > C SNP had a tendency of increased susceptibility to overall cancer (OR: 1.16, 95%CI: 0.98-1.38). The plausible outcome might be due to small sample sizes. The current investigation, in overall comparison, have suggested that HMGB1 rs1412125 T > C SNP

Table 5 Stratified analyses between high-mobility group box 1 rs1045411 C > T polymorphism and colorectal cancer risk by sex, age, body mass index, smoking status and alcohol consumption

Variable	HMGB1 rs1045411 C > T (case/control)[1]			Adjusted OR (95% CI); *P* value[2]			
	CC	CT	TT	Additive model	Homozygote model	Dominant model	Recessive model
Sex							
Male	388/522	186/245	30/32	0.99 (0.78-1.26); 0.951	1.18 (0.70-1.99); 0.547	1.01 (0.81-1.27); 0.904	1.18 (0.70-1.98); 0.536
Female	239/301	121/179	16/21	0.87 (0.65-1.17); 0.366	1.03 (0.52-2.05); 0.927	0.89 (0.67-1.18); 0.418	1.08 (0.55-2.14); 0.817
Age							
< 60	250/335	132/182	17/23	0.96 (0.73-1.26); 0.749	0.93 (0.51-1.72); 0.822	0.95 (0.74-1.24); 0.721	0.95 (0.52-1.73); 0.859
≥ 60	377/488	175/242	29/30	0.92 (0.72-1.18); 0.518	1.24 (0.70-2.21); 0.459	0.95 (0.75-1.21); 0.702	1.28 (0.72-2.25); 0.402
Smoking status							
Never	472/647	226/343	30/45	0.89 (0.72-1.10); 0.285	0.92 (0.56-1.49); 0.720	0.90 (0.73-1.09); 0.278	0.95 (0.59-1.54); 0.837
Ever	155/176	81/81	16/8	1.12 (0.76-1.63); 0.576	2.08 (0.86-5.05); 0.107	1.20 (0.84-1.74); 0.320	2.00 (0.83-4.83); 0.121
Alcohol consumption							
Never	522/736	250/382	38/46	0.92 (0.75-1.12); 0.397	1.15 (0.73-1.80); 0.547	0.94 (0.78-1.14); 0.544	1.18 (0.76-1.84); 0.463
Ever	105/87	57/42	8/7	1.12 (0.68-1.85); 0.650	0.81 (0.28-2.36); 0.692	1.08 (0.67-1.73); 0.767	0.77 (0.27-2.24); 0.635
BMI (kg/m^2)							
< 24	413/433	212/221	31/32	1.00 (0.79-1.26); 0.994	1.00 (0.60-1.68); 0.990	1.00 (0.80-1.25); 0.998	1.00 (0.60-1.67); 0.989
≥ 24	214/390	95/203	15/21	0.86 (0.64-1.17); 0.338	1.38 (0.69-2.75); 0.357	0.91 (0.69-1.21); 0.523	1.45 (0.73-2.87); 0.284

[1]The genotyping was successful in 980 (97.71%) cases, and 1300 (99.77%) controls for HMGB1 rs1045411 C > T.
[2]Adjusted for age, sex, body mass index, smoking status and alcohol consumption (besides stratified factors accordingly) in a logistic regression model.
OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; HMGB1: High-mobility group box 1.

could increase a susceptibility of CRC. In a subgroup analysis, our findings also found that HMGB1 rs1412125 T > C SNP could enhance an occurrence of CRC in BMI < 24 kg/m^2, non-drinker and ≥ 61 years subgroups. These observations were confirmed by calculating the power value (> 0.8). Based on the related large sample sizes included, these conclusions for the relationship between HMGB1 rs1412125 T > C SNP and the susceptibility of CRC may be more credible. In the future, more investigations are needed to confirm these associations.

The HMGB1 rs1045411 C > T SNP was also frequently explored the association of this polymorphism with cancer risk. Supic *et al*[44] first reported that HMGB1 rs1045411 C > T SNP was not associated with risk of oral squamous cell carcinoma. In addition, the association of HMGB1 rs1045411 C > T with CRC development was also irrelevant[28]. However, several case-control study indicated that this SNP was associated with the risk of cancer[20,26,31,45]. Therefore, in the future, the relationship of HMGB1 polymorphism with susceptibility to malignancy should be further investigated.

Luo *et al*[46] reported that HMGB1 could promote re-growth and metastasis of malignancy cells. A previous study suggested that over-expression of HMGB1 might be associated with a shorter overall survival time in CRC[47]. In colon cancer patients, Li *et al*[48] found that HMGB1 could be implicated in lymphangiogenesis and LNM *via* the HMGB1/VEGF/NF-κB pathway. Additionally, HMGB1 could suppress DCs in CRC cases[21]. HMGB1 disturbed host anti-cancer immunity and then increased the susceptibility of LNM[21]. In the current investigation, 1003 CRC cases were recruited to evaluate a correlation between HMGB1 two SNPs and the risk of LNM. However, we found that HMGB1 rs1412125 T > C and rs1045411 C > T SNP could not influence the risk of LNM. The possible explanation might be the moderate sample sizes in different subgroup. In the future, this issue should be explored with more studies.

There are some merits and limitations in our study. Firstly, this investigation was designed as a larger sample sizes study. Secondly, the sex and age were full-matched in this case-control study. Several limitations were related to bias of selection and included insufficient susceptibility factors. This study was designed as hospital-based, which could result in selection bias. For lack of data, we could not deduce the potential interaction of HMGB1 rs1412125 T > C and rs1045411 C

Table 6 Stratified analyses between high-mobility group box 1 polymorphisms and colorectal cancer risk by site of tumor

Genotype	Controls (*n* =1303)		Colon cancer cases (*n* = 431)		Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)[1]	*P* value[1]	Rectum cancer cases (*n* = 572)		Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)[1]	*P* value[1]
	n	%	*n*	%					*n*	%				
HMGB1 rs1412125 T > C														
TT	731	56.23	215	50.83	1.00		1.00		291	52.24	1.00		1.00	
TC	504	38.77	173	40.90	1.17 (0.93-1.47)	0.188	1.16 (0.92-1.46)	0.212	222	39.86	1.11 (0.90-1.36)	0.341	1.12 (0.91-1.39)	0.287
CC	65	5.00	35	8.27	1.83 (1.18-2.84)	0.007	1.81 (1.16-2.82)	0.009	44	7.90	1.70 (1.13-2.55)	0.010	1.69 (1.11-2.55)	0.014
TC + CC	569	43.77	208	49.17	1.24 (1.00-1.55)	0.053	1.23 (0.99-1.54)	0.064	266	47.76	1.17 (0.96-1.43)	0.114	1.19 (0.97-1.46)	0.097
TT + TC	1235	95.00	388	91.73	1.00		1.00		513	92.10	1.00		1.00	
CC	65	5.00	35	8.27	1.72 (1.12-2.63)	0.013	1.70 (1.10-2.61)	0.016	44	7.90	1.63 (1.10-2.42)	0.016	1.61 (1.07-2.40)	0.022
C allele	634	24.38	243	28.72					310	27.83				
HMGB1 rs1045411 C > T														
CC	627	63.98	279	65.96	1.00		1.00		348	62.48	1.00		1.00	
CT	307	31.33	123	29.08	0.86 (0.67-1.09)	0.208	0.85 (0.67-1.09)	0.200	184	33.03	1.03 (0.83-1.27)	0.812	1.01 (0.82-1.26)	0.900
TT	46	4.69	21	4.96	1.17 (0.69-1.97)	0.559	1.12 (0.66-1.90)	0.673	25	4.49	1.12 (0.68-1.82)	0.663	1.08 (0.65-1.78)	0.776
CT + TT	353	36.02	144	34.04	0.89 (0.71-1.12)	0.324	0.88 (0.70-1.12)	0.294	209	37.52	1.04 (0.84-1.27)	0.734	1.02 (0.83-1.26)	0.846
CC + CT	934	95.31	402	95.04	1.00		1.00		532	95.51	1.00		1.00	
TT	46	4.69	21	4.46	1.23 (0.73-2.06)	0.435	1.18 (0.70-1.99)	0.535	25	4.49	1.11 (0.68-1.80)	0.686	1.07 (0.65-1.76)	0.788
T allele	399	20.36	165	19.50					234	21.01				

[1]Adjusted for age, sex, smoking status, alcohol use and body mass index status.
OR: Odds ratio; CI: Confidence interval; HMGB1: High-mobility group box 1.

> T SNPs with lifestyles. Finally, in this investigation, only two HMGB1 SNPs were included for study. However, other SNPs in *HMGB1* gene should not been ignored. And the interaction of HMGB1 rs1412125 T > C and rs1045411 C > T SNPs with other HMGB1 SNPs also should be considered.

Table 7 Logistic regression analyses of association between high-mobility group box 1 single nucleotide polymorphisms and lymph node status of colorectal cancer patients

Genotype	Positive (*n* = 518)		Negative (*n* = 485)		Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)[1]	*P* value
	n	%	*n*	%				
HMGB1 rs1412125 T > C								
TT	259	50.88	247	52.44	1.00		1.00	
TC	208	40.86	187	39.70	1.06 (0.82-1.38)	0.661	1.05 (0.81-1.37)	0.700
CC	42	8.25	37	7.86	1.08 (0.67-1.74)	0.744	1.09 (0.68-1.76)	0.712
TC + CC	250	49.12	224	47.56	1.06 (0.83-1.37)	0.626	1.06 (0.82-1.36)	0.650
TT + TC	467	91.75	434	92.14	1.00		1.00	
CC	42	8.25	37	7.86	1.06 (0.67-1.67)	0.820	1.07 (0.67-1.70)	0.776
C allele	292	28.68	261	27.71				
HMGB1 rs1045411 C > T								
CC	315	61.89	312	66.24	1.00		1.00	
CT	169	33.20	138	29.30	1.21 (0.92-1.60)	0.167	1.21 (0.92-1.59)	0.182
TT	25	4.91	21	4.46	1.18 (0.65-2.15)	0.591	1.19 (0.65-2.17)	0.578
CT + TT	194	38.11	159	33.76	1.21 (0.93-1.57)	0.156	1.20 (0.93-1.57)	0.167
CC + CT	484	95.09	450	95.54	1.00		1.00	
TT	25	4.91	21	4.46	1.11 (0.61-2.01)	0.738	1.12 (0.62-2.03)	0.718
T allele	219	21.51	180	19.11				

[1]Adjusted for age, sex, alcohol use and smoking status.
OR: Odds ratio; CI: Confidence interval; HMGB1: High-mobility group box 1.

CONCLUSION

To the best of our knowledge, this case-control study first confirms the possible relationship of HMGB1 rs1412125 T > C polymorphism with an increased susceptibility of CRC. In the future, more studies should be conducted to explore this SNP in relation to CRC development.

Table 8 Logistic regression analyses of association between high-mobility group box 1 single nucleotide polymorphisms and lymph node status of colorectal cancer in different region

Genotype	Colon cancer								Rectum cancer							
	Positive (*n* = 205)		Negative (*n* = 226)		Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)[1]	*P* value[1]	Positive (*n* = 313)		Negative (*n* = 259)		Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)[1]	*P* value[1]
	n	%	*n*	%					*n*	%	*n*	%				
HMGB1 rs1412125 T > C																
TT	95	47.03	120	54.30	1.00		1.00		164	53.42	127	50.80	1.00		1.00	
TC	87	43.07	86	38.91	1.28 (0.86-1.91)	0.232	1.29 (0.86-1.93)	0.216	121	39.41	101	40.40	0.93 (0.65-1.32)	0.676	0.92 (0.65-1.32)	0.657
CC	20	9.90	15	6.79	1.68 (0.82-3.47)	0.157	1.69 (0.82-3.48)	0.157	22	7.17	22	8.80	0.77 (0.41-1.46)	0.430	0.78 (0.41-1.49)	0.455
TC + CC	107	52.97	101	45.70	1.34 (0.91-1.96)	0.136	1.35 (0.92-1.98)	0.126	143	46.58	123	49.20	0.90 (0.64-1.26)	0.538	0.90 (0.64-1.26)	0.531
TT + TC	182	90.10	206	93.21	1.00		1.00		285	92.83	228	91.20	1.00		1.00	
CC	20	9.90	15	6.79	1.51 (0.75-3.04)	0.248	1.51 (0.75-3.03)	0.252	22	7.17	22	8.80	0.80 (0.43-1.48)	0.478	0.81 (0.44-1.51)	0.509
C allele	127	31.44	116	26.24					165	26.87	145	29.00				
HMGB1 rs1045411 C > T																
CC	127	62.87	152	68.78	1.00		1.00		188	61.24	160	64.00	1.00		1.00	
CT	66	32.67	57	25.79	1.39 (0.91-2.12)	0.133	1.41 (0.92-2.16)	0.117	103	33.55	81	32.40	1.08 (0.76-1.55)	0.667	1.08 (0.75-1.55)	0.685
TT	9	4.46	12	5.43	0.90 (0.37-2.20)	0.813	0.90 (0.37-2.21)	0.814	16	5.21	9	3.60	1.51 (0.65-3.52)	0.336	1.57 (0.67-3.68)	0.297
CT + TT	75	37.13	69	31.22	1.30 (0.87-1.95)	0.201	1.32 (0.88-1.98)	0.182	119	38.76	90	36.00	1.13 (0.80-1.59)	0.503	1.13 (0.80-1.60)	0.503
CC + CT	193	95.54	209	94.57	1.00		1.00		291	94.79	241	96.40	1.00		1.00	
TT	9	4.46	12	5.43	0.81 (0.34-1.97)	0.645	0.81 (0.33-1.97)	0.644	16	5.21	9	3.60	1.47 (0.64-3.39)	0.364	1.53 (0.66-3.55)	0.320
T allele	84	20.79	81	18.33					135	21.99	99	19.80				

[1]Adjusted for age, sex, smoking status, alcohol use and body mass index status.
OR: Odds ratio; CI: Confidence interval; HMGB1: High-mobility group box 1.

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