Original Article

High expression of *MAGE-C1* gene in colorectal cancer is associated with its poor prognosis

Yu Tian[1], Ping Liang[2], Lihua Zhang[3], Xiufen Zhang[4], Xiaoli Wang[1], Yufen Jin[2], Xiaowei Qi[1], Yankui Liu[1]^

[1]Department of Pathology, Affiliated Hospital of Jiangnan University, Wuxi, China; [2]Wuxi Medical College, Jiangnan University, Wuxi, China; [3]Department of Gastrointestinal Surgery, Zhongshan Hospital Xiamen University, Xiamen, China; [4]Wuxi Cancer Institute, Affiliated Hospital of Jiangnan University, Wuxi, China

Contributions: (I) Conception and design: Y Tian, Y Liu; (II) Administrative support: X Qi; (III) Provision of study materials or patients: P Liang, X Wang, Y Jin; (IV) Collection and assembly of data: Y Jin, X Wang; (V) Data analysis and interpretation: L Zhang, X Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yankui Liu; Xiaowei Qi. Department of Pathology, Affiliated Hospital of Jiangnan University, No. 1000, Hefeng Road, Wuxi 214122, China. Email: lykyoung@126.com; qixiaowei97@126.com.

Background: The aim of this study was to explore the relationship between melanoma antigen gene C1 (*MAGE-C1*) expression and the prognosis for colorectal cancer (CRC), and to establish a mathematical model to comprehensively evaluate the prognosis of patients with CRC.

Methods: *MAGE-C1* was selected by bioinformatics for its greater expression differences in CRC patients. Immunohistochemistry (IHC) was used to detect the expression level of *MAGE-C1* in tissue samples of 156 patients with CRC. Kaplan-Meier analysis was employed to assess the relationship between *MAGE-C1* and the prognosis of patients with CRC. Univariate and multivariate Cox regression models analyzed the factors affecting the prognosis of CRC patients. Also, the clinicopathological characteristics of patients and genes with clinical concern were integrated to establish a model to comprehensively predict the prognosis of patients with CRC.

Results: *MAGE-C1* was found to be highly expressed in 28.8% of CRC patients. *MAGE-C1* expression was associated with tumor size, number, and metastasis. Survival analysis showed that CRC patients with high expression of *MAGE-C1* had a poor prognosis. Regression analysis demonstrated that *MAGE-C1* protein status, T stage, differentiation, Kirsten rat sarcoma (*KRAS*) status, and v-RAF murine sarcoma viral oncogene homolog B1 (*BRAF*) status were the independent factors influencing the overall survival of patients with CRC. Meanwhile, *MAGE-C1* combined with clinicopathological characteristics and hotspot gene mutations could be used to evaluate the prognosis of CRC.

Conclusions: Our study shows that *MAGE-C1* is differentially expressed in patients with CRC and affects the prognosis of patients. The combination of *MAGE-C1*, clinicopathological characteristics, and genes with clinical concern can be used to assess the prognosis of CRC.

Keywords: Melanoma antigen gene C1 (*MAGE-C1*); colorectal cancer (CRC); Kirsten rat sarcoma (*KRAS*); prognosis

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^ ORCID: 0000-0002-7295-4757.

Introduction

The melanoma antigen gene (*MAGE*) family, a member of the cancer-testis antigen (CTA) family (1), has attracted increasing attention from researchers. Due to MAGE protein's immunogenicity, they can be used as new markers for tumor immunotherapy (2). MAGE family proteins have a certain relationship with the aggressiveness of tumors, including poor clinical prognosis, acceleration of tumor progression, and metastasis (3-5). In recent years, numerous in-depth studies have been performed on the MAGE family proteins in tumor immunotherapy and prognosis although many challenges remain.

Several studies have shown an association of the MAGE family proteins to the prognosis of various tumors, such as non-small cell lung cancer (6), melanoma (3,5), breast cancer (7), and prostate cancer (8), and therefore, they are considered to be markers for poor prognosis of many tumors. However, as tumorigenesis is affected by many factors, such as genetic changes and individual patient differences, linking individual MAGE antigen with poor survival rates in tumors is insufficient evidence to conclusively show that their expression promotes aggressive tumor growth or that they are associated with chemorefractory disease.

Mori *et al.* first observed the expression of *MAGE* in colorectal cancer (CRC) (9). Recently, it has been reported that *MAGE-A3* (10), *MAGE-D4* (11), *MAGE-A9* (12) are highly expressed in colorectal cancer, and the former two are associated with poor prognosis of colorectal cancer, but the mechanism underlying the occurrence is unclear. Further studies may be helpful to utilize these proteins as targets for immunotherapy or targeted therapies.

MAGE-C1, also known as *CT7* or *CT7.1*, is a member of *MAGE-C* subfamily which is clustered on the X-chromosome and the protein which encodes contains a large number of unique short repeats ahead of the *MAGE* homologous sequence and thus is therefore about 800 amino acids longer than other MAGE proteins. Current studies have focused *MAGE-C1* on multiple myeloma to explore its value in malignant cell typing (13), and other studies have found it to be associated with poor prognosis of multiple myeloma (14). Some studies have found its abnormal expression in ovarian cancer (15), others in breast cancer and associated with poor prognosis in breast cancer patients (16). However, few studies have reported its expression in colorectal cancer.

In our study, we aimed to establish a model that utilize expression of *MAGE-C1*, clinicopathological characteristics and genes with clinical concern of CRC to predict the prognosis of CRC. First, the genes with significant expression differences in CRC were analyzed by bioinformatics methods through The Cancer Genome Atlas (TCGA) database. MAGE-C1, an abnormally expressed protein, was identified for its significant expression differences. Then, we investigated the expression of *MAGE-C1* in CRC using immunohistochemistry (IHC) and analyzed its relationship with the clinicopathological characteristics of CRC and the related hotspot gene changes. At last, these 3 data sets were adopted to establish a model to comprehensively evaluate the combined effect of *MAGE-C1* and clinicopathological characteristics and hotspot gene changes on the prognosis of CRC patients.

We present the following article in accordance with the REMARK reporting checklist (available at https://dx.doi.org/10.21037/jgo-21-739).

Methods

Bioinformatics analysis

The "edgeR" and "limma" packages in R software (version3.6.2, https://www.r-project.org; The R Foundation for Statistical Computing, Vienna, Austria) were used to evaluate differentially expressed genes (DEGs) of CRC in TCGA (https://portal.gdc.cancer.gov/). The gene expression profiles of CRC were downloaded from TCGA. RNA sequencing (RNA-seq) count data on CRC and corresponding clinical information were freely downloaded by R package GDCRNATools (17). There were 408 CRC samples, including 376 tumor and 32 normal tissues. The DeSeq2 package (18) was used to identify the DEGs genes in CRC. DEGs were defined as genes with P value <0.05 and |fold change (FC)| ≥2. The DEGs were also clustered using the package "Heatmap" and were visualized as Volcano Plots using the "ggplot2" package.

Collection of sample cases with CRC

This study collected 156 paraffin-embedded specimens from the Affiliated Hospital of Jiangnan University, Jiangsu, China, from March 2014 to January 2015. There were 85 males and 71 females, aged 31–89 years, with a median age of 70 years. The clinicopathological data of the above cases were summarized. All the above cases were treated in accordance with Chinese CRC diagnosis and treatment

protocols and standards. The data of Kirsten rat sarcoma (*KRAS*), v-RAF murine sarcoma viral oncogene homolog B1 (*BRAF*), and human epidermal growth factor receptor 2 (*HER2*) genes were procured from routine testing items in the pathology department of the hospital. The follow-up time was considered to be from surgical removal of the patient's tumor tissue to the patient's tumor-related death. The collection and processing of specimens were performed after informed consent of the patients was obtained. The study was approved by the Ethics Committee of the Affiliated Hospital of Jiangnan University (No. 2014-012-001). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

IHC analysis

MAGE-C1 primary antibody (rabbit monoclonal: EPR18067) was purchased from Abcam (Cambridge, UK), and DAB color reagent was purchased from Gene Technology Shanghai Co., Ltd, (Shanghai, China). The specimens were immediately immersed in 10% neutral formalin fixative and fixed from 4 to 16 hours after collection. After collection by the pathologist, the specimens were dehydrated, embedded, and then cut into sections, each 4 μm in thickness. The sections were then deparaffinized with xylene, dehydrated with gradient ethanol, immersed in citric acid sodium citrate buffer for antigen repair, blocked with 3% normal goat serum, and incubated with the primary antibody for 1 hour and the secondary antibody for 30 minutes. Finally, they were stained with DAB. The IHC results were interpreted by 2 pathologists. In this study, a semiquantitative method was used to evaluate the results of IHC. The brown color of the cell membrane and/or cytoplasm indicated positive MAGE-C1 protein IHC. The intensity of staining was divided into 4 levels: no staining (–), 0 points; weak positive (+), 1 point; medium intensity (++), 2 points; and strong positive (+++), 3 points. The density of MAGE-C1-positive cells was divided into 4 levels: no staining, 0 points; proportion of positive cells >0 and ≤10%, 0.1 points; proportion of positive cells >10% and ≤50%, 0.5 points; and proportion of positive cells greater than 50%, 1 point.

For semiquantitative scoring, an H score was used. The relative formula was the following: H = staining intensity × staining density. The cutoff value was set at 1.0 according to the clinical testing standard of the pathology department. When the value was above and equal to the cutoff value, this indicated high expression; when the value was lower than the cutoff value, this indicated low expression.

Statistical analysis

All statistical analyses in this study were carried out using R statistical software. A chi-square test was used to assess the correlation between *MAGE-C1* expression and the clinical characteristics of the patients. The effect of *MAGE-C1* expression on the overall survival rate was analyzed by the Kaplan-Meier method, and the difference was ascertained via a log-rank test. The risk factors used in prognoses for CRC patients were analyzed by Cox regression models. A nomogram was constructed based on the results of the multivariate analysis using the "rms" package in R version 3.6.2. The reported statistical significance levels were all two sided, with the statistical significance set at a P value <0.05.

Results

Identification of MAGE-C1 in CRC by bioinformatics analysis

The messenger RNA (mRNA) data of CRC tissue were downloaded from TCGA database, and totally 18,473 genes were included for analysis by DESeq2 after merging of the same genes. We found that 2,806 genes were upregulated in CRC tissues and 2,618 genes were downregulated (*Figure 1*: heat map, volcano plot and violin plot) after threshold value analysis (P<0.01, |fold change| >2). We observed that *MAGE-C1* (LogFC =8.87; false discovery rate =1.99×10^{-7}) was one of the most significant outlier genes in the list.

The MAGE-C1 expression in CRC and its relationship with clinicopathological characteristics, CRC hotspot gene mutations, and prognosis

We detected *MAGE-C1* expression in paraffin-embedded tissues of 156 patients with CRC. IHC results showed that *MAGE-C1* was mainly expressed in the cell membrane and cytoplasm, as shown in *Figure 2*; *MAGE-C1* was not expressed in normal colorectal mucosa controls. The proportions of high and low *MAGE-C1* expression in CRC were 28.8% (45/156) and 71.2% (111/156), respectively. The *MAGE-C1* expression in CRC was related to the cancer T stage (P=0.010) and M stage (P<0.001) of patients, which means tumor invasion, and metastasis were related to the expression of *MAGE-C1*, as shown in *Table 1*.

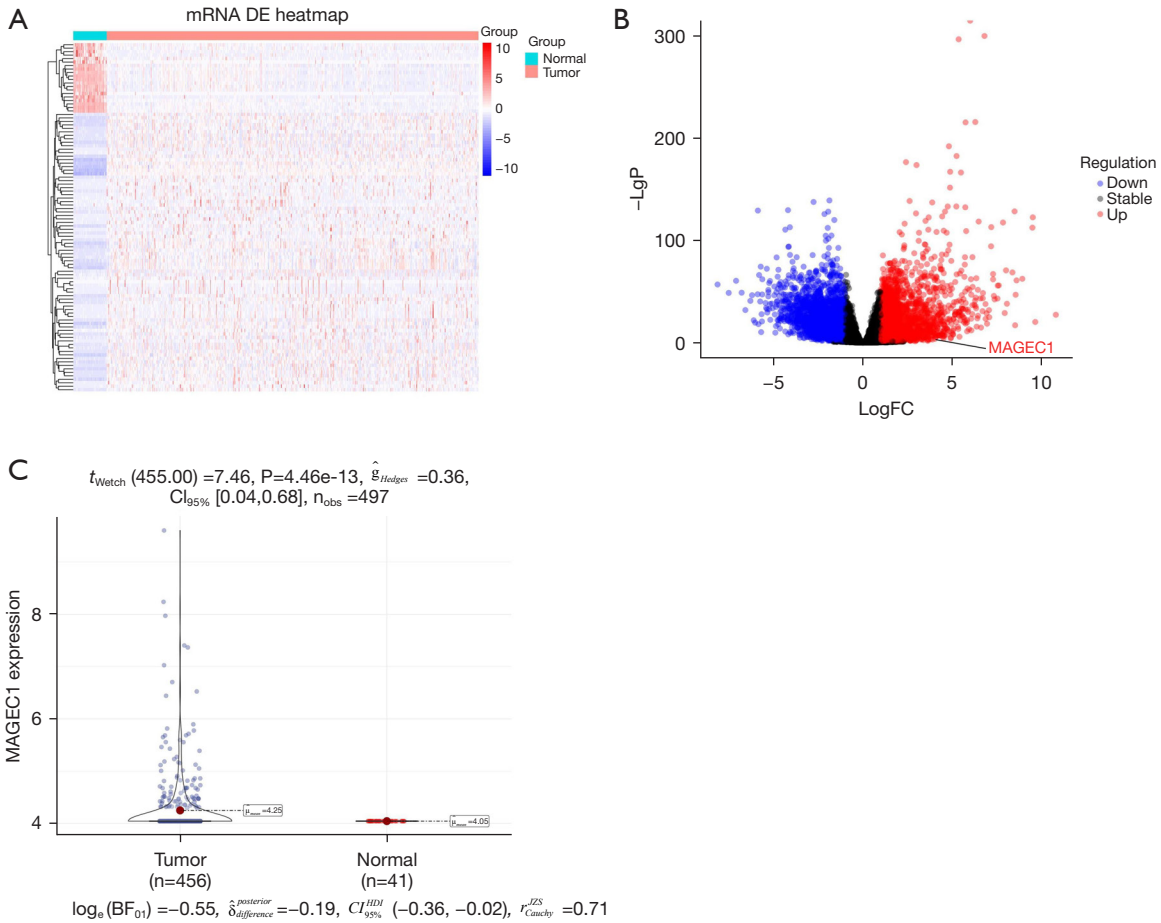

Figure 1 Bioinformatics analysis to screen differentially expressed genes in colorectal cancer. (A) Heat map of gene expression; (B) volcano plot of gene expression; (C) violin plot.

Kaplan-Meier survival analysis showed that the median overall survival duration of patients with high and low *MAGE-C1* expression was 31.1 and 53.5 months, respectively, and the difference was statistically significant (P<0.001), as shown in *Figure 3*. *MAGE-C1* outlier expression was positively associated with reduced survival duration.

Univariate and multivariate Cox regression analysis suggested that, compared to CRC patients with *MAGE-C1* high expression, patients with *MAGE-C1* low expression had better prognosis [hazard ratio (HR) =0.34, P<0.001]; compared to CRC patients with *KRAS* and *BRAF* mutations, patients with *KRAS* wild type (HR =0.31, P<0.001) and *BRAF* wild type (HR =0.32, P<0.05) had better prognosis. Compared to CRC patients with T3/T4 stage, patients with T1/T2 stage had a better prognosis (HR =0.22, P<0.05); compared to CRC patients within well or moderate differentiation, patients within poor differentiation had a worse prognosis (HR =2.21, P<0.05), as shown in *Table 2*.

MAGE-C1 combined with clinicopathological characteristics and hotspot gene mutations in predicting survival rate of patients

We designed a model that used the clinicopathological characteristics of patients and the information about CRC hotspot gene mutations to predict patient survival. First, the Cox regression model was employed to weight the scores of various factors and assign values to each factor, and then these values were added to acquire the total value. Next, we used this total value to calculate the patient's corresponding predicted survival time in the model. The model is shown in *Figure 4A*. Finally, we tested the reliability and validity of the model. The results showed that the calibration chart was consistent with the primary cohort. The 3-year and 5-year OS nominal map

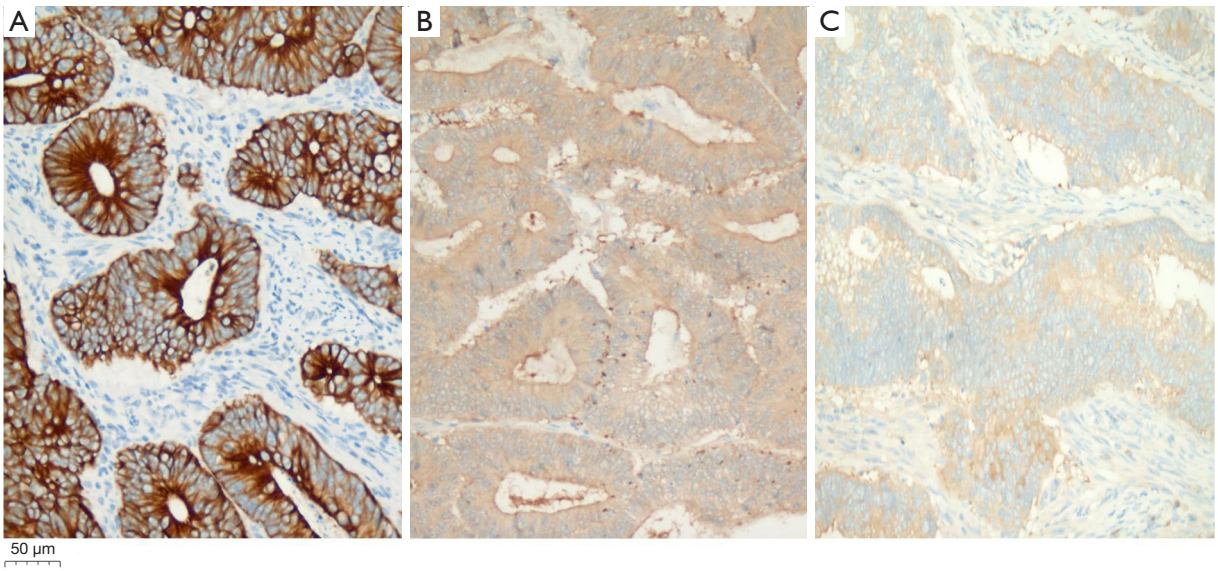

Figure 2 *MAGE-C1* expression in colorectal cancer (IHC stain, ×200). (A) High expression, score 3.0; (B) close to threshold value, score 1.0; (C) low expression, score 0.3. *MAGE-C1*, melanoma antigen gene C1; IHC, immunohistochemistry.

predictions and actual observations were basically in line with those of the International Association for the Study of Lung Cancer (IASLC) verification cohort, as shown in *Figure 4B*.

Discussion

The worldwide incidence and mortality of CRC rank third and second among all cancers, respectively. There are about 1.8 million new cases reported and about 881 thousand people died due to CRC in 2018 (19). Survival rates for CRC patients can vary based on several factors. For some patients at an early stage, surgical removal of these tumors can sometimes eliminate cancer, which can improve the 5-year survival rate for these patients (20). In terms of late-stage patients, standard radiation therapy, chemotherapy, and targeted therapy have prolonged the survival time of patients and improved the quality of life of patients. Moreover, tumor immunotherapy has gained popularity, and its application, such as in the form of the checkpoint inhibitors of pembrolizumab and nivolumab, is being gradually broadened in clinical practice (21). Some studies have highlighted the role of immunotherapy in specific types of CRC (22). MAGE proteins, as targets for cancer immunotherapy, have also attracted increasing interest among researchers. Indeed, studies have shown that the MAGE protein could be used for immunotherapy and targeted therapy (23).

MAGE-C1, a CTA, is widely expressed in multiple myeloma. More than 85% of symptomatic patients with multiple myeloma show expression of *MAGE-C1* in the bone marrow and peripheral blood (24). Furthermore, *MAGE-C1* could be used to determine the types of malignant cells in multiple myeloma (13), and targeting *MAGE-C1/CT7* expression has been shown to increase cell sensitivity to the proteasome inhibitor bortezomib (25). *MAGE-C1* is expressed in a certain subset of ovarian carcinomas with no expression in borderline tumors or ovarian carcinomas of mucinous histology (15). Although the effect of some MAGE protein expression on patient survival has been studied, there is a lack of ample research on the effect of MAGE-C1 protein on the prognosis of CRC patients.

Our analysis of 156 cases with CRC showed that patients with high *MAGE-C1* expression presented a worse prognosis than those with low expression. Overexpression of MAGE family proteins has been associated with the poor prognosis of many cancers in several studies. For example, *MAGE-A12* was related to the high TNM staging of gastric cancer, and was demonstrated to be an independent indicator of poor prognosis in patients with gastric cancer (26). The expression of *MAGE-A1-6* in the peritoneal lavage after gastric cancer surgery is correlated with the patient's reduced disease-free survival rate, indicating its association with tumor

Table 1 *MAGE-C1* expression and patients' characteristics

Characteristics	No.	High	Low	P value
Age, years				0.993
≤60	41	12	29	
>60	115	33	82	
Gender				0.866
Female	71	20	51	
Male	85	25	60	
T stage				0.010
T1–2	37	4	33	
T3–4	119	41	78	
N stage				0.426
N0	96	25	71	
N1–N2	60	20	40	
M stage				0.001
M0	124	27	97	
M1	32	18	14	
Differentiation				0.309
Poorly	39	14	25	
Well/moderately	117	31	86	
HER2				0.984
Wild	152	44	108	
Mutation	4	1	3	
KRAS				0.086
Wild	101	24	77	
Mutation	55	21	34	
BRAF				0.424
Wild	143	43	100	
Mutation	13	2	11	
PIK3CA				0.998
Wild	132	38	94	
Mutation	24	7	17	

MAGE-C1, melanoma antigen gene C1; *HER2*, human epidermal growth factor receptor 2; *KRAS*, Kirsten rat sarcoma; *BRAF*, v-RAF murine sarcoma viral oncogene homolog B1; *PIK3CA*, Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha.

recurrence (27). MAGE family proteins were also found to be related to other solid tumors. For example, *MAGE-A3* was shown to be a poor prognostic indicator of non-small cell lung cancer (28), *MAGE-A3* and *A6* were found to be correlated to the poor prognosis of specific types of breast cancer (7), while *MAGE-A1* and *A10* were associated with the poor prognosis of ovarian cancer (29). However, the impact of *MAGE-C1* protein on the prognosis of CRC has

not been extensively reported.

This study observed that the high expression of *MAGE-C1* in CRC was related to higher TNM staging, which is similar to the relationship between *MAGE-A12* and TNM staging in gastric cancer (26). The increase in TNM staging indicated tumor progression to a higher degree and also suggested *MAGE-C1* functions to be a driver of tumorigenesis in CRC. Studies have demonstrated that cell infiltration with high expression of *MAGE-C2* to be increased in cell lines cultured *in vitro* (30).

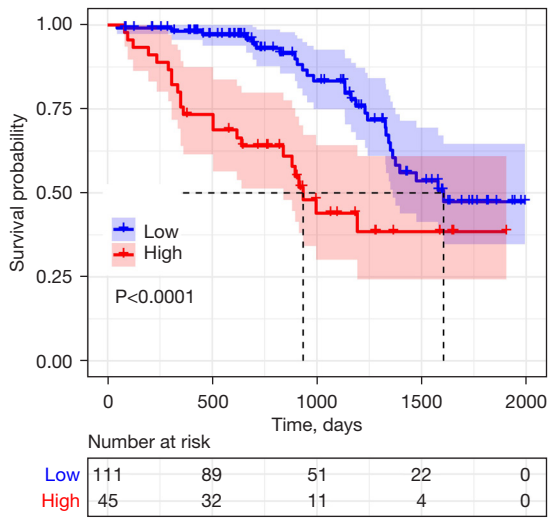

Figure 3 Overall survival curve of patients with low expression of *MAGE-C1* versus those with high expression. *MAGE-C1*, melanoma antigen gene C1.

The bias produced by a single indicator to predict the survival of cancer patients is often large (31). Multiple indicators to predict the survival of CRC often produce better results. According to the expression level of *MAGE-C1*, patient's clinicopathological characteristics, genes with clinical concern, and patient survival data, we designed a model that integrated the clinicopathological characteristics and genes with clinical concern of patients with CRC to predict their survival rate. Although the model still needs further improvement, it can be used as an important tool for the clinicopathological evaluation of patient prognosis. Compared with other methods, our model may be more amenable to clinicians because this method only needs to collect clinicopathological characteristics and genes with clinical concern of patients, which are genes recommended for testing in clinical CRC diagnosis and treatment guidelines. The calculation method of the patient's expected survival is simple and can be integrated into one program. Thus overall, the method is relatively time-saving and efficient.

This study has some limitations. The data collected were only from 156 patients with CRC. Only 7

Table 2 Univariate and multivariate Cox model analysis of clinical factors and the prognosis of patients

Characteristics	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age (≤60/>60 years)	1.57	0.86–2.88	0.144	1.11	0.56–2.17	0.771
Gender (male/female)	0.68	0.39–1.18	0.172	0.84	0.44–1.60	0.590
T stage (T1 & T2/T3 & T4)	0.11	0.04–0.32	0.001	0.22	0.07–0.67	0.007
N stage (N0/N1 & N2)	0.24	0.13–0.42	0.001	0.69	0.34–1.41	0.307
M stage (M0/M1)	0.19	0.11–0.34	0.001	0.52	0.25–1.05	0.069
Differentiation (poorly/well and moderately)	3.60	2.02–6.43	0.001	2.21	1.04–4.68	0.038
MAGEC1 (low/high)	0.34	0.20–0.60	0.001	0.34	0.18–0.64	0.001
HER2 (wild/mutation)	0.51	0.16–1.63	0.255			
KRAS (wild/mutation)	0.46	0.26–0.80	0.006	0.31	0.16–0.61	0.001
BRAF (wild/mutation)	0.46	0.22–0.94	0.032	0.32	0.14–0.75	0.008
PIK3CA (wild/mutation)	0.62	0.31–1.23	0.173	0.80	0.38–1.69	0.562

The characteristics with P≤0.2 in univariate analysis were included in the multivariate analysis. *MAGE-C1*, melanoma antigen gene C1; HER2, human epidermal growth factor receptor 2; *KRAS*, Kirsten rat sarcoma; *BRAF*, v-RAF murine sarcoma viral oncogene homolog B1; *PIK3CA*, Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha.

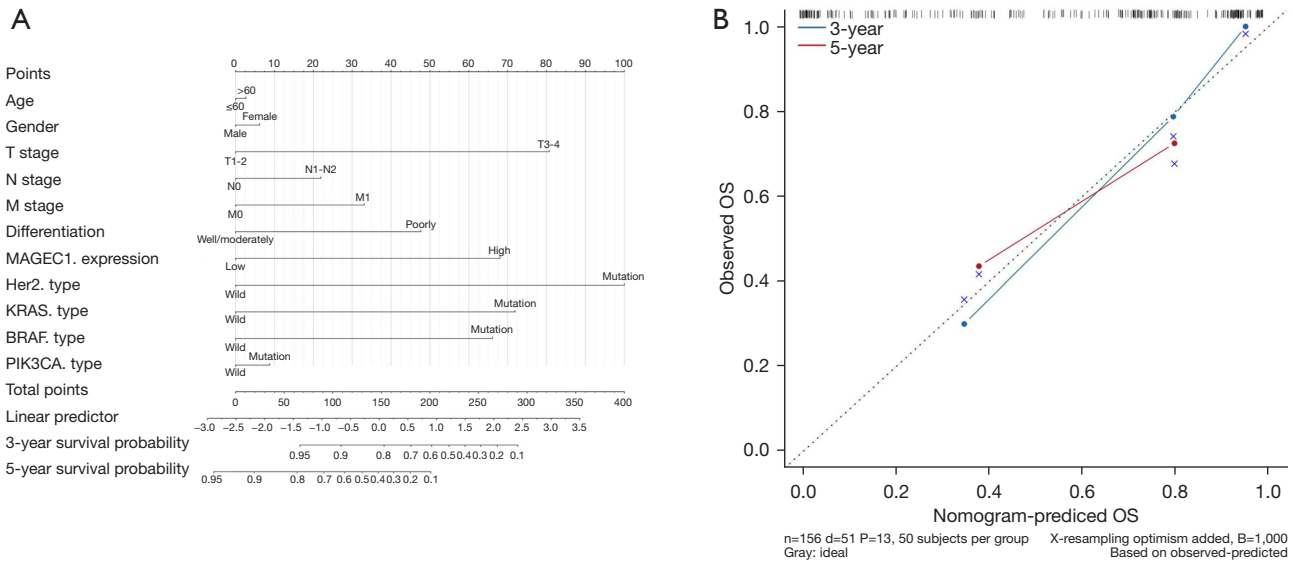

Figure 4 Survival prediction model of colorectal cancer associated with *MAGE-C1*. (A) Prognostic nomogram for colorectal cancer based on *MAGE-C1*, clinical features and CRC related hotspot gene status; (B) time-dependent receiver operating characteristic curves for the combination of *MAGE-C1* based prognostic score and clinical-pathological, hotspot gene variance. *MAGE-C1*, melanoma antigen gene C1.

clinicopathological parameters and 6 genes with clinical concern were introduced into the prediction model. Thus, the accuracy and effectiveness of the model need to be further validated. Besides, we are not clear how *MAGE-C1* affects CRC progression, and that's also what we need to do next.

Conclusions

Overall, *MAGE-C1* is a poor prognostic indicator of CRC. Its pathogenicity in CRC needs to be further studied. Compared with using a single index to predict the prognosis of CRC, it is more effective in predicting the prognosis of CRC through its use of a mathematical model that incorporates multiple parameters.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Affiliated Hospital of Jiangnan University (No. 2014-012-001). All patients gave written informed consent.

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