



Plasma soluble human leukocyte antigen G predicts the long-term prognosis in patients with colorectal cancer

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Background: Colorectal cancer (CRC) is the third most common tumor in the world. It is crucial to further screen for indicators that are strictly related to long-term prognosis. Human leukocyte antigen G (HLA-G) is closely involved in tumor development. This study aims to evaluate the long-term predictive value of soluble HLA-G (sHLA-G) in CRC through a double-center retrospective study.

Methods: Patients who underwent radical CRC surgery in two hospitals from April 2010 to March 2015 were included. Baseline data of the patients were collected. The patients' preoperative baseline plasma sHLA-G level was detected. According to whether they survived during five years of follow-up, these patients were divided into two groups. Univariate and multivariate analysis were used to find factors associated with survival. The receiver operation curve (ROC) was performed to analyze the relationship between sHLA-G level and five-year survival, and the cutoff value was obtained. The baseline data and follow-up results of the two groups of patients were compared, and the Kaplan-Meier survival curve was used to analyze the difference in the long-term prognosis of the two groups of patients.

Results: A total of 1,037 cases were included and followed up for more than five years. Three hundred two cases (29.1%) died during the five-year follow-up. The baseline data of the survival group and the death group showed that the baseline level of sHLA-G in the survival group was significantly lower than the death group (41.4 ± 16.9 vs. 64.7 ± 23.2 , $P < 0.05$). Univariate and multivariate analyses suggest that age, differentiation, family history, TNM stage, and baseline sHLA-G levels are important factors affecting the survival of CRC patients. The area under ROC of sHLA-G with five-year survival is 0.766, and the cutoff value is 50.8 U/mL. The specificity at this point is 78.1%, and the sensitivity is 72.3%. The Kaplan-Meier survival curve showed that the five-year prognosis of patients in the low-level group was better than that in the high-level group.

Conclusions: Lower baseline sHLA-G level predicts better prognosis during a five-year follow-up in colorectal cancer patients.

Keywords: Soluble human leukocyte antigen G (sHLA-G); colorectal cancer (CRC); prognosis

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Introduction

Colorectal cancer (CRC) is the third most common tumor in the world, ranking fourth in the cause of cancer death (1). Although 60% to 70% of colorectal cancer patients are

diagnosed with locally advanced tumors at the initial diagnosis, half of the patients will eventually relapse or metastasize after radical resection (2,3). Although the effectiveness of the current comprehensive treatment of

colorectal cancer is significantly improved compared with before, and the five-year survival rate is also significantly improved. However, due to the large population with CRC, there are still many patients affected by poor prognosis. Therefore, finding suitable long-term prognostic indicators is essential for monitoring patients with a high risk of poor prognosis and, therefore, to improve prognosis. Many studies have shown that changes in the body's immune status and inflammatory response are strictly related to the occurrence, development, and prognosis of tumors (4,5). Human leukocyte antigen G (HLA-G) belongs to non-classical HLA class I molecules, and is one of the immunosuppressive molecules for innate immunity and acquired immunity. The initial transcription product can be encoded to produce seven isomers, including four membrane-bound types (HLA-G1–HLA-G4) and three soluble types (HLA-G5–HLA-G7). Also, HLA-G1 can be hydrolyzed by matrix metalloproteinases to form another soluble HLA-G1 molecule (6). HLA-G molecules can bind to their corresponding receptors, including immunoglobulin-like transcript 2 (immunoglobulin-like transcript 2, ILT2), immunoglobulin-like transcript 4 (immunoglobulin-like transcript 4, ILT4), and Killer cell immunoglobulin-like receptor 2DL4 (KIR2DL4) participates in tumor immune escape by inhibiting the killing of natural killer (NK), inhibiting the proliferation of effector T cells and inducing the production of Treg cells and abnormally expressed HLA-G is often associated with various malignant tumors (7). This study aims to evaluate the long-term predictive value of soluble human leukocyte antigen G (soluble HLA-G, sHLA-G) in colorectal cancer through a two-center retrospective study since no research has investigate the long-term predictive value of this molecule in patients with CRC.

We present the following article in accordance with the REMARK reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-2211>).

Methods

Study population

Patients who underwent radical colorectal cancer surgery in two hospitals from April 2010 to March 2015 were enrolled according to the inclusion criteria: (I) pathologically confirmed colon or rectal cancer during or after surgery; (II) surgery and other anti-tumor treatment for the first time; (III) acquisition of frozen plasma before surgery; (IV) age ≥ 18 years old; (V) completed more than five years of follow-

up or died within five-year follow-up; exclusion criteria: (I) connective tissue disease; (II) severe heart failure; (III) severe renal function decline; (IV) active liver disease. All procedures performed in this study were in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Shaanxi Provincial People's Hospital and the Ethics Committee of Shaanxi Fourth People's Hospital. The ethics committee waived informed consent.

Data collection

The Patient's baseline data, including demographic data, preoperative blood test indicators, test results, surgical and pathological results, and five-year follow-up results, were collected. The patients' preoperative plasma sHLA-G baseline level was detected. According to whether they survived at five years of follow-up, they were divided into two groups. Univariate and multivariate analysis is used to factors associated with the rate of five-year survival. The ROC curve was generated to correlate sHLA-G with the rate of five-year survival, and the cutoff value of sHLA-G for predicting five-year survival was obtained. According to this cutoff value, patients were divided into high-level and low-level sHLA-G groups, and baseline data of the two groups were compared. The Kaplan-Meier survival curve was used to analyze the difference of long-term prognosis between the two groups.

Samples test

For each patient before surgery, 10 mL of blood was acquired, centrifuged at $1,800 \times g$ for 10 minutes at room temperature to separate plasma, and stored frozen at $-80^\circ C$ until use. The concentration of plasma sHLA-G was detected with a specific enzyme linked immunosorbent assay (ELISA) kit (BioVendor Laboratory Medicine, Inc., Brno, Czech Republic), and operated according to the manual instructions. The detection limit of this kit was 0.6 U/mL. Other baseline test results include white blood cell count, lymphocyte count, neutrophil count, red blood cell count, hemoglobin concentration, platelet count, urine routine, fecal occult blood, liver function, kidney function, electrolytes, carcinoembryonic antigen (CEA) before the operation was collected and repeated at follow-up.

Follow-up

All patients were followed up at three months, six months, and one year after surgery and then followed up once a year.

Follow-up contents included: laboratory test described as before, liver ultrasound, colonoscopy. Abdominal computed tomography (CT) was repeated for patients with lymph node metastasis detected in the preoperative examination or during operation. Other information, including survival or not, second-time surgery was obtained.

Statistical analysis

Statistical processing was performed using SPSS17.0 statistical software. Data that conformed to the normal distribution were expressed as mean \pm standard deviation, and comparison between groups was conducted using the student test; those that did not conform to the normal distribution were expressed as median, and comparison between groups was conducted using the rank-sum test. The qualitative data are expressed in numerical values and percentages, and comparisons between groups are performed using the X^2 test or Fisher's exact test. The ROC curve was used to correlate sHLA-G with the rate of five-year survival. Kaplan-Meier survival curve was used to compare the prognosis between groups with the different plasma levels of sHLA-G. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics and follow-up outcome

According to the exclusion criteria, 1,037 patients with colorectal cancer were included in the final analysis (Table 1). The patients in this study were 34 years old to 72 years old, with an average of 62.3 ± 12.7 years old, including 592 elderly patients (≥ 60 years old) and 445 young and middle-age patients (< 60 years old). Almost all this population was male (58.1%), and over 50% of these patients were diagnosed with rectal cancer (56.1%). As for Tumor Node Metastasis (TNM) stages, 32.5% of patients were at stage II, 50% were at stage III. The diameter of the tumor in 1/3 patients was less than 4 cm. See Table 1 for details. The majority (71.7%) of patients received adjuvant chemoradiation, but the proportion of elderly patients receiving adjuvant chemoradiation was lower than non-elderly patients (386/592 vs. 358/445, $X^2 = 29.132$, $P < 0.001$).

Univariate and multivariate analysis of five-year survival of colorectal cancer patients

During the five-years follow-up, 302 patients (29.1%) died,

735 patients (70.9%) survived, and 73 patients (7.0%) were diagnosed colorectal cancer again. Patients were divided into two groups: patients who survived (survival group) and patients who died (death group) during follow-up. The baseline data of the two groups of patients are compared (Table 2). After the initial univariate analysis, a multivariate analysis was performed (Table 3). The age of the patients in the survival group was significantly lower than the death group, and the proportion of male patients was higher in the survival group. The proportion of patients at TNM stage I/II in the survival group was significantly higher than that in the death group. The patients in the death group had a higher proportion of first-degree relatives of their family history of colorectal cancer, and their plasma sHLA-G level was significantly higher than those in the survival group, and their blood CEA level was significantly higher than those in the survival group. From these results, we select parameters with a P value not greater than 0.1 for further univariate and multivariate analysis. The results are shown in Table 3. It can be seen that age, tumor differentiation, family history, TNM stage, and preoperative plasma sHLA-G levels are predictive factors for the five-year prognosis of colorectal cancer patients.

The cutoff point of soluble human leukocyte antigen G

A receiver operating characteristic (ROC) curve was used to evaluate the ability of the plasma level of sHLA-G discriminated between patients who survived and patients who did not survive during the five-year follow-up (Figure 1). The area under the ROC curve was 0.766, and the best cutoff value of sHLA-G for predicting the five-year survival of colorectal cancer patients was 50.8 U/mL. The specificity at this point was 78.1%, and the sensitivity was 72.3%. According to the cut-off value, the patients were divided into high-level group (sHLA-G ≥ 50.8 U/mL) and low-level group (sHLA-G < 50.8 U/mL). A comparison of baseline data between these two groups (Table 4) shows that preoperative sHLA-G has a strong relationship with patients' conditions. Low-level patients have smaller tumors, a higher proportion of stage I and stage II, and a lower proportion of positive family history CRC.

Comparison of five-year follow-up outcomes of patients with different levels of sHLA-G

The comparison of the follow-up outcomes between the two groups found the proportion of disease-free survival,

Table 1 Baseline characteristics

Items	Results
Age (years)	62.3±12.7
Sex (n, %)	
Male	603 (58.1)
Female	434 (41.9)
Rectal (n, %)	582 (56.1)
Colon (n, %)	455 (43.9)
Diameter of tumor (n, %)	
≥4 cm	413 (39.8)
<4 cm	624 (60.2)
Differentiation (n, %)	
Low	282 (27.2)
High-moderate	755 (72.8)
T stage (n, %)	
1–2	475(45.8)
3–4	562 (54.2)
N stage (n, %)	
0	487 (47.0)
1–2	550 (53.0)
M stage (n, %)	
0	993 (95.8)
1	44 (4.2)
Tumor stage (n, %)	
I	144 (13.9)
II	337 (32.5)
III	519 (50.0)
IV	37 (3.6)
WBC (×10 ⁹ /mL)	5.8±2.4
NEU (×10 ⁹ /mL)	3.5±1.4
Hb (g/L)	129.6±17.2
PLT (×10 ⁹ /mL)	163.5±48.1
ALT (U/L)	31.2±13.6
Cr (μmol/L)	71.9±16.4
TC (mmol/L)	5.7±1.5
TG (mmol/L)	1.9±1.1
CEA (ng/mL)	7.2±2.7

Table 1 (continued)**Table 1** (continued)

Items	Results
Hs-CRP (mg/L)	4.9±2.5
Smoke (n, %)	297 (28.6)
Alcohol (n, %)	411 (39.6)
FH (n, %)	137 (13.2)
R&C (n, %)	744 (71.7)
sHLA-G (U/L)	48.2±13.8

WBC, white blood cell; NEU, neutrophils; Hb, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; Cr, creatine; TC, total cholesterol; TG, triglyceride; CEA, cancer embryo antigen; hs-CRP, high sensitivity C reaction protein; FH, family history; R&C, radiotherapy or chemotherapy; sHLA-G, soluble human leukocyte antigen G.

recurrence, and death of patients in the low-level group during five-year follow-up was significantly lower than those in the high-level group. Furthermore, the success rate of second surgery in the low-level group was higher than that in the high-level group (28/35 vs. 22/38), see *Table 5* for details. The Kaplan-Meier survival curve showed that the prognosis of patients in the low-level group was significantly better than that in the high-level group (*Figure 2*).

Discussion

In this study, we retrospectively analyzed the data of 1,037 patients who underwent radical colorectal cancer resection in the two hospitals for five years and found the baseline plasma sHLA-G level was strongly associated with the five-year survival after surgery. We found that age, differentiation, family history, TNM stage, and preoperative baseline level of sHLA-G are essential factors related to the survival of colorectal cancer patients. In this study, the optimal cutoff value for sHLA-G to predict five-year survival after surgery was 50.8 U/mL, with a specificity of 78.1% and a sensitivity of 72.3%. According to this point, the patients were divided into a low-level group and a high-level group, which showed the differentiation level, TNM stage, and five-year survival rate of the low-level group were better than those of the high-level group. The Kaplan-Meier survival curve showed that the five-year prognosis of patients in the low-level group was better than that in the high-level group.

The incidence and death of CRC in China have increased in recent years. 2015 Chinese cancer statistics

Table 2 Comparison of baseline data between group of survival and group of death

Items	Group of survival (n=735)	Group of death (n=302)	t/X ² value	P value
Age (years)	60.1±13.6	67.7±14.8	-7.965	<0.001
Male (n, %)	447 (60.8)	156 (51.7)	7.381	0.007
Rectal (n, %)	402 (54.7)	180 (59.6)	2.095	0.148
Colon (n, %)	333 (45.3)	122 (40.4)		
Diameter of tumor (n, %)			0.209	0.647
≥4 cm	296 (40.3)	117 (38.7)		
<4 cm	439 (59.7)	185 (61.3)		
T stage (n, %)			2.009	0.1556
1-2	347 (47.2)	128 (42.4)		
3-4	388 (52.8)	174 (57.6)		
N stage (n, %)			59.185	<0.001
0	289 (39.3)	198 (65.6)		
1-2	446 (60.7)	104 (34.4)		
M stage (n, %)				
0	706 (96.1)	287 (95.0)	0.550	0.489
1	29 (3.9)	15 (5.0)		
Tumor stage (n, %)			39.887	<0.001
I/II	387 (52.7)	94 (31.1)		
III/IV	348 (47.3)	208 (68.9)		
WBC (10 ⁹ /mL)	5.9±2.5	5.6±2.3	1.796	0.073
NEU (10 ⁹ /mL)	3.5±1.4	3.5±1.4	0.000	1.000
Hb (g/L)	130.2±17.8	128.1±18.3	1.712	0.087
PLT (10 ⁹ /mL)	167.2±52.5	154.5±55.1	1.236	0.217
ALT (U/L)	30.4±11.9	33.1±12.6	-1.208	0.227
Cr (μmol/L)	71.3±15.3	73.6±16.1	-1.883	0.060
TC (mmol/L)	5.7±1.6	5.7±1.8	0.000	1.000
TG (mmol/L)	1.9±0.9	1.9±1.2	0.000	1.000
CEA (ng/mL)	7.1±2.5	7.4±2.9	-1.674	0.095
Hs-CRP (ng/L)	5.0±2.4	4.7±2.6	1.784	0.075
Smoke (n, %)	219 (29.8)	78 (25.8)	1.649	0.199
Alcohol (n, %)	281 (38.2)	130 (43.0)	2.074	0.150
FH (n, %)	74 (10.1)	63 (20.9)	21.746	<0.001
R&C (n, %)	533 (72.5)	211 (69.9)	0.741	0.389
sHLA-G (U/L)	41.4±16.9	64.7±23.2	-17.989	<0.001

WBC, white blood cell; NEU, neutrophils; Hb, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; Cr, creatine; TC, total cholesterol; TG, triglyceride; CEA, cancer embryo antigen; hs-CRP, high sensitivity C reaction protein; FH, family history; R&C, radiotherapy or chemotherapy; sHLA-G, soluble human leukocyte antigen G.

Table 3 Factors associated with death during 5-years follow-up

Items	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.572 (1.108–1.836)	0.008	1.602 (1.115–1.918)	0.007
Male	1.114 (0.947–1.427)	0.205	1.200 (0.985–1.513)	0.186
Differentiation	1.402 (1.074–1.739)	0.017	1.483 (1.104–1.805)	0.021
FH	1.684 (1.121–1.968)	0.028	1.539 (1.117–1.933)	0.031
TNM stage	2.015 (1.328–2.415)	0.006	2.022 (1.441–2.571)	0.009
sHLA-G	1.906 (1.377–2.305)	0.010	1.784 (1.319–2.283)	0.012

FH, family history; sHLA-G, soluble human leukocyte antigen G.

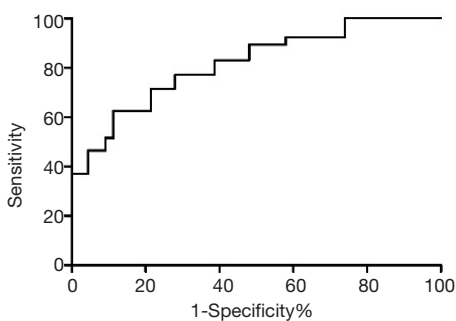


Figure 1 ROC curve of soluble human leukocyte antigen G predicting five-year survival. ROC, receiver operation curve.

showed that the incidence and mortality of colorectal cancer in China ranks fifth among all malignant tumors, including 376,000 new cases and 191,000 deaths. The incidence of CRC in urban areas is much higher than that in rural areas, and most patients are already in the middle and late stages when they are diagnosed (8). However, with the wide use of colonoscopy, the improvement of surgical methods, and the progress of postoperative adjuvant radiotherapy and chemotherapy, the current treatment effectiveness of colorectal cancer and its prognosis have been significantly improved compared with the previous situation. However, due to the large population in China, the number of patients with colorectal cancer is enormous. Although more patients undergo radical surgery for colorectal cancer, many patients still have a poor prognosis. Therefore, how to predict the patient's prognosis more accurately is crucial to monitor high-risk patients and help discover adverse events and provide effective intervention early. Previous studies have found some useful predictors. First of all, some traditional predictors, including the tumor differentiation, TNM stage, and the age of the patient, are strongly associated with

patients' prognosis. Other parameters including changes in several neutrophils in blood indicators (9), neutrophil/lymphocyte ratio (10), plasma fibrinogen (11), serum thymidine kinase 1 (12), peripheral blood lymphocytes, and mononuclear cell ratio (13), microRNA (14), etc., also have certain predictive values for the postoperative prognosis of colorectal cancer patients. However, these predictors are not closely related to the mechanism of tumorigenesis and development and are easily disturbed by many factors, including neutrophils, which are easily disturbed by the infection status of patients. Therefore, there are still many studies to explore more suitable blood indicators for the long-term prognosis of colorectal cancer. HLA-G is one of the most critical immunosuppressive molecules in the human body. It is only expressed at the maternal-fetal interface, and some immune exempted tissues under physiological conditions (15), while abnormally expressed HLA-G is often associated with various malignant tumors, viral infections, and inflammations (16-18). Earlier studies have shown that 70.7% of colorectal cancer tissues express HLA-G, and the expression status of HLA-G is closely related to the prognosis of patients.

Further studies have found that plasma sHLA-G can be used as colorectal cancer independent prognostic factors for patients (19,20). Also, Zhu *et al.* found that serum sHLA-G levels can be used for differential diagnosis of benign and malignant colorectal diseases, suggesting that HLA-G can be used as a biomarker for the diagnosis and prognosis of colorectal cancer (21). However, there are several problems with these studies. Some studies have a smaller sample size, some studies only aim to assess the severity of the disease, and some studies have relatively shorter follow-up duration. At present, there are consensus and guidelines regarding the screening and early diagnosis of colorectal cancer (22,23).

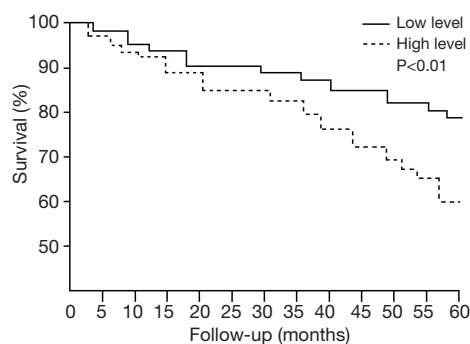
Table 4 Comparison of baseline data of patients with different level of sHLA-G

Items	High level (n=415)	Low level (n=622)	t/X ² value	P value
Age (years)	63.1±13.6	61.8±12.8	1.563	0.119
Male (n, %)	219 (52.8)	384 (61.7)	8.221	0.004
Rectal (n, %)	239 (57.6)	343 (55.1)	0.605	0.437
Colon (n, %)	176 (42.4)	279 (44.9)		
Diameter of tumor (n, %)			11.969	0.001
≥4 cm	192 (46.3)	221 (35.5)		
<4 cm	223 (53.7)	401 (64.5)		
T stage (n, %)			13.696	<0.001
1–2	161 (38.8)	314 (50.5)		
3–4	254 (61.2)	308 (49.5)		
N stage (n, %)			8.454	0.004
0	172 (41.4)	315 (50.6)		
1–2	243 (58.6)	307 (49.4)		
M stage (n, %)			0.037	0.848
0	398 (95.9)	595 (95.7)		
1	17 (4.1)	27 (4.3)		
Tumor stage (n, %)			44.601	<0.001
I	39 (9.4)	105 (16.9)		
II	108 (26.0)	229 (36.8)		
III	241 (58.1)	278 (44.7)		
IV	27 (6.5)	10 (1.6)		
WBC (10 ⁹ /mL)	5.7±2.2	5.9±2.4	–1.359	0.175
NEU (10 ⁹ /mL)	3.4±1.5	3.6±1.6	–2.022	0.044
Hb (g/L)	128.5±18.9	130.3±19.6	–1.470	0.142
PLT (10 ⁹ /mL)	164.4±50.2	162.9±49.3	0.477	0.634
ALT (U/L)	32.7±14.1	30.2±13.9	2.708	0.007
Cr (μmol/L)	73.5±18.8	70.8±17.4	2.370	0.018
TC (mmol/L)	5.4±1.6	5.9±1.9	–4.417	<0.001
TG (mmol/L)	1.8±0.8	2.0±1.3	–2.800	0.005
CEA (U/L)	7.0±2.0	7.3±1.9	–2.439	0.015
Hs-CRP (ng/L)	5.1±2.8	4.8±2.6	1.765	0.078
Smoke (n, %)	129 (31.1)	168 (27.0)	2.022	0.155
Alcohol (n, %)	175 (42.2)	236 (37.9)	1.859	0.173
FH (n, %)	73 (17.6)	64 (10.3)	11.572	0.001
R&C (n, %)	262 (63.1)	482 (77.5)	25.319	<0.001
sHLA-G (U/L)	56.8±15.5	42.5±14.7	15.016	<0.001

sHLA-G, soluble human leukocyte antigen G; WBC, white blood cell; NEU, neutrophils; Hb, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; Cr, creatine; TC, total cholesterol; TG, triglyceride; CEA, cancer embryo antigen; hs-CRP, high sensitivity C reaction protein; FH, family history; R&C, radiotherapy or chemotherapy.

Table 5 Five years follow-up outcome in high-level group and low-level group

Events	High-level group (n=415)	Low-level group (n=622)	t/ χ^2 value	P value
Disease-free survival (n, %)	229 (55.2)	433 (69.6)	22.463	<0.001
Death (n, %)	167 (40.2)	135 (21.7)	41.437	<0.001
Recurrence (n, %)	38 (9.2)	35 (5.6)	4.739	0.030
Second surgery (n, %)	22 (5.7)	28 (4.5)	4.125	0.042

**Figure 2** The Kaplan-Meier survival curve shows that the prognosis of patients in the low-level group is significantly better than that in the high-level group.

For the long-term prognosis of patients with colorectal cancer after radical surgery, the study is still inadequate. Simultaneously, due to the wide use of colonoscopy and the gradual increase in people's awareness of physical examination, the diagnostic rate of colorectal cancer of early and middle stages has dramatically increased, resulting in the current demographic characteristics of colorectal cancer patients differing from the those of the past (1-3), which also affects the value of traditional risk factors or predictors. Therefore, it is necessary to evaluate further the existing predictors for the new research results.

This study confirmed that sHLA-G could be used as a long-term prognostic indicator for patients with colorectal cancer after radical surgery. These findings are consistent with the results of other studies (IJK). Simultaneously, however, the sample size involved in this study is larger, and the follow-up time is longer. The ability of sHLA-G levels to predict prognosis during follow-up has already been revealed at the end of 3 years follow-up after surgery (survival rate 76.2% vs. 85.1%, $P=0.032$). From this result,

we can select patients at elevated risk of poor prognosis to develop a personalized follow-up plan.

Moreover, our research results showed that the preoperative baseline level of sHLA-G is not only related to five-year survival, but also has a statistically significant correlation with disease-free survival, tumor recurrence, and re-operation. Therefore, for colorectal cancer, patients with a high baseline level of sHLA-G, regular colonoscopy, and other examinations are of clinical significance. Limitations of this study: Due to the smaller sample size, this study cannot combine sHLA-G with other predictive indicators to establish a predictive score, and its predictive validity may be relatively weak. Concurrently, because most colorectal cancer patients are middle-aged, and older adults and the middle-aged and older adults often have other diseases and receive certain drug treatment. This study did not analyze the effect of drugs on the circulating level of sHLA-G. Future research should focus on these points.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-2211>). The authors have no conflicts of interest to declare.

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. All procedures performed in this study were in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Shaanxi Provincial People's Hospital and the Ethics Committee of Shaanxi Fourth People's Hospital. The ethics committee waived informed consent.

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