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Original Article

Expression of IL-33 in colorectal cancer and its association with clinical features

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Abstract: Tumor immunotherapy has strong potential worldwide. IL-33 mostly acts as a danger signal from damaged cells, and has recently been discovered as a influencing factor in the process of tumor immunity. The aim of the study is to discover the expression of IL-33 in colorectal cancer (CRC) and its association with clinical features and prognosis. We found that the positive expression rate of IL-33 in tumor tissues was significantly lower than that in peritumoral tissues (38.78% vs. 63.75%, Pearson χ^2 = 10.989 P = 0.001). In addition, serum IL-33 levels in moderate or poor differentiation CRC cases were significantly higher than that in well differentiation cases. Serum IL-33 level in colon cancer cases was also significantly higher than that in rectal cancer cases (P < 0.01). Moreover, that combination of serum IL-33, CEA and CA19-9 may improve diagnostic efficiency for colorectal cancer. In conclusion, IL-33 may associate with tumor progress in CRC, and showed improved value in CRC diagnosis.

Keywords: Interleukin-33, colorectal cancer, clinical features

Introduction

Colorectal cancer (CRC) is the third most common type of cancer in the world. The present mainstream methods of treatment include surgery, chemotherapy and radiation [1]. The conventional therapies have greatly induce tumor inhibition, but with side effects and drug resistance in the long term. So the improvements of overall survival and quality of life of CRC patients have certain limitations [2]. In recent years, tumor immunotherapy has put up the characteristics with strong potential and widespread acceptance worldwide [3]. A deeper understanding of the mechanisms of tumorigenesis and tumor prognosis may facilitate the achievement of tumor immunotherapy.

Interleukin-33 (IL-33) is a member of the interleukin-1 (IL-1) cytokine family. IL-33 is mainly expressed in epithelial cells, endothelial cells, and smooth muscle cells [4]. IL-33 mostly acts as a danger signal from damaged cells, and is identified as an inflammatory cytokine. Inhibition of IL-33 involved pathway may have anti-inflammatory effects [5]. IL-33 has recently been discovered as an influencing factor in the process of tumor immunity, and is implicated in cancer pathogenesis. The aim of the study is to discover the expression of IL-33 in colorectal cancer and its association with clinical features and prognosis.

Materials and methods

Tissue microarray

The colon cancer tissue microarray was purchased from Shanghai Biochip Company (HColA180Su09), which included paired tumor and peritumoral tissues from 80 colon cancer patients and 18 single colon cancers. All patients underwent surgical colon resection between July 2006 and May 2007. Patients ranged in age from 24 to 90 years old, with the median age of 71 years. All the patients were followed up to August 2014. None of these patients received pre-operative chemotherapy or radiotherapy. All cases were confirmed as colon cancer by pathologists. Tumor-node-metastasis (TNM) stages were classified according to the American Joint Committee on Cancer Criteria 7th version.

Immunohistochemistry

Immunohistochemical staining was performed using the Elivision™ method. The IL-33 antibody (1:450 dilution, Sigma-Aldrich, USA) was the primary antibody in this study. The secondary antibody and diaminobenzidine (DAB) color-developing agent solution were provided by DAKO Company (Glostrup, Denmark). Tissue microarray was dewaxed in dimethylbenzene, rehydrated in graded ethanol solution of gradient concentration. Antigen retrieval was performed at 100 degrees centigrade for 30 min in citrate solution (10 mmol/L, pH 6.0). Then the tissue microarray was incubated for 15 min in 0.3% hydrogen peroxide solution to block endogenous peroxidase activity, followed by overnight incubation with the polyclonal rabbit antibody against human IL-33 in a humidified chamber at 4 degrees centigrade. After incubation for 30 min with the secondary antibody at room temperature 25°C, Tissue microarray was stained with DAB, counterstained with hematoxylin. Finally, tissue microarray was dehydrated and mounted. Negative controls were treated similarly except for phosphate buffer solution instead of primary antibody.

Evaluation of IL-33 expression

IL-33 immunostaining intensities were assessed by professional pathologists in the Third Affiliated Hospital of Soochow University. Tissues with medium brown or blue staining were considered as positive. Every sample in the tissue microarray with more than 50 percent positive staining area was considered as positive ultimately.

Serum samples

Serum samples of colorectal cancer patients from the third affiliated hospital of Soochow University were collected. 121 Samples were collected during Feb 2014 and May 2015, including 72 male patients and 49 female patients, with the age of (62.55 ± 11.70) years old. 53 samples were from colon cancer, and 68 were from rectal cancer. Inclusion criteria: The patients in this study didn't accept prior hormonal therapy, chemotherapy or radiotherapy, with normal cardiac and renal function. Exclusion criteria: The patients were complicated with primary tumors located in other part of body, or internal diseases that out of control. Meanwhile, 81 serum samples from healthy examined people and 33 from intestinal polyp patients were also collected. All patients and healthy examined people had their serum collected in early morning of the first day in hospital. All the colorectal cancer patients had their clinical features collected, such as gender, age, tumor diameter, degrees of differentiation, lymphatic metastasis, TNM staging, location and histological type.

Detection of serum samples

The detection of serum IL-33 was performed by ELISA (enzyme linked immunosorbent assay) method, according to the instruction and operation manual. The microplate reader (Multiskan GO, Thermo Fisher Scientific, Massachusetts, USA) was used for the measurement of absorbance of all samples. The standard curve was drawn by the standard concentration as the abscissa, and absorbance as the ordinate. So the serum IL-33 concentrations were worked out from the standard curve. The CEA (carcinoembryonic antigen) and CA19-9 (carbohydrate antigen 19-9) of the samples were detected by Cobas e601 automatic electrochemical luminescence immunity analyzer (Roche Company, Basel, Switzerland). All the operation sequences were according to the operating instructions for the equipment.

Statistical analyses

SPSS Statistics 19.0 (IBM Company, Chicago, USA) was used in data analysis. Pearson's chi-square test was utilized to compare the constituent ratio in order to analyze the relationship of IL-33 or serum IL-33 with clinical features. Overall survival (OS) of various clinical features was compared using Kaplan-Meier and log-rank tests. The Cox proportional hazards model was performed to estimate hazard risk (HR) with 95% confidence intervals (CI) of the linking strength between different clinical characteristics, IL-33 expression death risks. The *P*-value of < 0.05 was considered statistically significant. All statistical tests were two-sided. GraphPad Prism 6.02 (CA 92037, USA) was utilized for creating statistical graphs.

Results

IL-33 expression in tumor and peritumoral colon tissues

As shown in **Figure 1**, IL-33 staining was predominantly observed in cytoplasm and nucleus of peritumoral cells (**Figure 1C** and **1D**), while

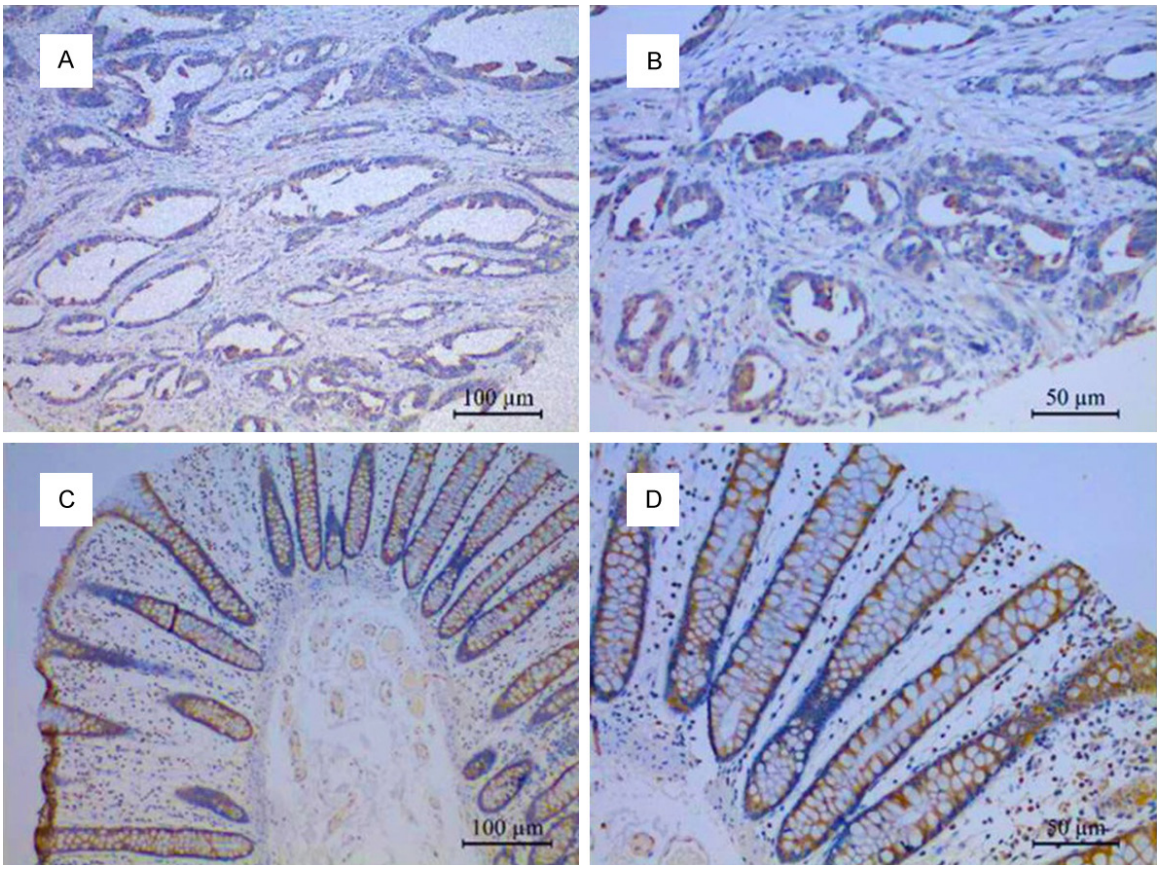

Figure 1. Immunohistochemical staining of IL-33 in tumor tissue (A and B) and peritumoral tissue (C and D) Magnification: (A, C) 100 ×, (B, D): 200 ×.

Table 1. Comparison of IL-33 expression in colon tumor tissues and peritumoral tissues

	Cases	IL-33 Positive	IL-33 Negative
Tumor tissues	98	38 (38.78%)	60
Peritumoral tissues	80	51 (63.75%)	29

$\chi^2 = 10.989$, P = 0.001.

no or weak staining was observed in the tumor tissues (**Figure 1A** and **1B**). As is shown in **Table 1**, Among 98 cases of tumor tissues, 38 cases had positive IL-33 staining. Among 80 cases of peritumoral tissues, 51 cases had positive IL-33 staining. The positive expression rate of IL-33 in tumor tissues was significantly lower than that in peritumoral tissues (38.78% vs. 63.75%, Pearson $\chi^2 = 10.989$ $P = 0.001$).

Relationship of IL-33 expression and clinicopathological parameters

To study the relationships between IL-33 expression and patients' clinicopathological parameters, we divided cases into subgroups by various clinicopathological parameters, respectively. The various clinicopathological parameters consist of patients' gender, age, tumor diameter, pathological grading, tumor location, depth of invasion, lymphatic metastasis, distant metastasis and AJCC TNM Staging (7th edition). The positive and negative expression counts were worked out in each subgroup respectively. Pearson's chi-square test or Fisher's exact test were used to compare the positive rates of IL-33 in each subgroup. As is shown in **Table 2**, cases with pathological grading I, II and III were 10/15, 25/68 and 3/15, respectively, with corresponding positive expression rate of 66.67%, 36.76% and 20%, respectively, with a statistically significant difference ($P = 0.027$). Conclusion could be drawn from the data that the higher level of pathological grading, the lower expression of IL-33 in tumor tissues. Nevertheless, there were not any relationships between IL-33 expression and patients' any other clinicopathological parameter ($P > 0.05$).

Table 2. Correlation between IL-33 expression and clinicopathological parameters

Parameters	Cases	Positive	Negative	Pearson χ^2	*P*
Gender				0.582	0.445
Male	52	22	30		
Female	46	16	30		
Age				0.880	0.348
≥ 60 yrs	77	28	49		
< 60 yrs	21	10	11		
Tumor diameter*				0.178	0.673
≥ 5 cm	48	17	31		
< 5 cm	48	19	29		
Pathological grading				N/A	0.027**
I	15	10	5		
II	68	25	43		
III	15	3	12		
Tumor location*				0.132	0.964
Transverse	25	9	16		
Descendents	37	15	22		
Ascendants	34	13	21		
Depth of invasion*				N/A	1.000
Serosa reached	7	3	4		
Serosa unreached	87	33	54		
Lymphatic metastasis*				3.357	0.067
No	58	26	32		
Yes	38	10	28		
Distant metastasis				N/A	1.000
No	95	37	58		
Yes	3	1	2		
AJCC TNM Staging*				N/A	0.282
I	6	3	3		
II	52	23	29		
III	35	9	26		
IV	3	1	2		

Notes: *Very few cases censored because parameters cannot retrieved, **statistical significance. Abbreviations: AJCC, American Joint Committee on Cancer. N/A, not applicable, because Fisher's exact test was applicable only.

Prognostic values of IL-33 and other clinicopathological parameters in colon caner

As is shown in **Figure 2**, patients with TNM stages of III & IV showed significantly worse survival compared with those of I & II ($P = 0.0003$, log-rank test) (**Figure 2A**). Patients with TNM stages of I and II had a 60% reduction in risk of death (Hazard ratio 0.3999, 95% confidence interval: 0.1922~0.6014), compared with those with TNM stages of III and IV.

Patients with positive IL-33 expressions have no significant different overall survival compared with those with negative IL-33 expressions ($P = 0.013$, log-rank test) (**Figure 2B**). The univariate and multivariate Cox's proportional hazards regression model were used to analyze the clinicopathological parameters for overall survival. As shown in **Table 3**, the Cox regression univariate analysis showed that distant metastasis was a negative prognostic factor for OS (overall survival), [$P < 0.01$, HR (hazard ratio) = 13.246, 95% CI (confidence interval): 3.721~47.152]. AJCC TNM staging III/IV versus I/II was also a negative prognostic factor for OS ($P < 0.01$, HR = 2.396, 95% CI: 1.430~4.016). Multivariate analysis showed that distant metastasis was a negative factor for OS ($P = 0.002$, HR = 7.841, 95% CI: 2.095~29.352), AJCC TNM staging III/IV versus I/II was also a negative factor for OS ($P = 0.003$, HR = 2.594, 95% CI: 1.394~4.827).

Serum IL-33 level in colorectal cancer and control group

As is shown in **Figure 3**, serum IL-33 level in CRC (colorectal cancer) group was 172.44 (108.08, 321.57) pg/mL, which was 67.31 (37.72, 130.44) pg/mL in intestinal polyp group, 71.73 (36.80, 85.53) pg/mL in healthy control group. The serum IL-33 level in CRC group was significantly higher than that in intestinal polyp and healthy control group ($Z = 4.938$, $P < 0.01$ and $Z = 8.921$, $P < 0.01$, respectively). The serum IL-33 level in intestinal polyp group had no significantly difference in comparing with healthy control group ($Z = 1.015$, $P = 0.31$).

Serum IL-33 level in CRC patients and its correlation with clinical features

The CRC group was divided into various subgroups by different clinical features, such as

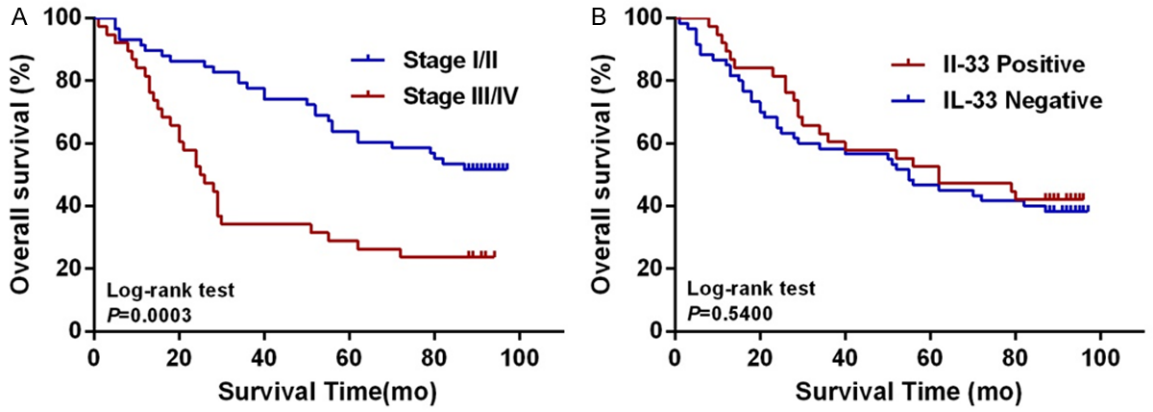

Figure 2. Kaplan-Meier survival curves of colon cancer patients based on TNM stages and IL-33 expressions. Patients with TNM stages of III/IV showed significantly worse survival compared with those of I/II (P = 0.0003, log-rank test) (A). Patients with positive IL-33 expressions have no significant different overall survival compared with those with negative IL-33 expressions (P = 0.5400, log-rank test) (B).

Table 3. Univariate and multivariate analysis of clinicopathological parameters for overall survival

Clinicopathological parameters	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender (male vs. female)	1.033 (0.619~1.725)	0.900	0.807 (0.449~1.449)	0.473
Age (≥ 60 yrs vs. < 60 yrs)	1.541 (0.780~3.044)	0.213	1.323 (0.652~2.682)	0.438
Tumor diameter (≥ 5 cm vs. < 5 cm)	1.051 (0.631~1.752)	0.847	1.227 (0.709~2.123)	0.465
Pathological grading (Grade III vs. Grade I/II)	1.552 (0.785~3.067)	0.206	1.556 (0.741~3.267)	0.243
Serosa invasion (reached vs. unreached)	0.656 (0.262~1.642)	0.368	0.591 (0.228~1.529)	0.278
Distant metastasis (Yes vs. No)	13.246 (3.721~47.152)	< 0.01*	7.841 (2.095~29.352)	0.002*
AJCC TNM staging (III/IV vs. I/II)	2.396 (1.430~4.016)	< 0.01*	2.594 (1.394~4.827)	0.003*
IL-33 expression (positive vs. negative)	1.178 (0.695~1.997)	0.543	0.904 (0.515~1.586)	0.724

Notes: *Statistical significance. **Parameter "Lymphatic metastasis" was censored because of its strongly linearly association with parameter "AJCC TNM staging". Abbreviations: HR, hazard ratio. CI, confidence interval.

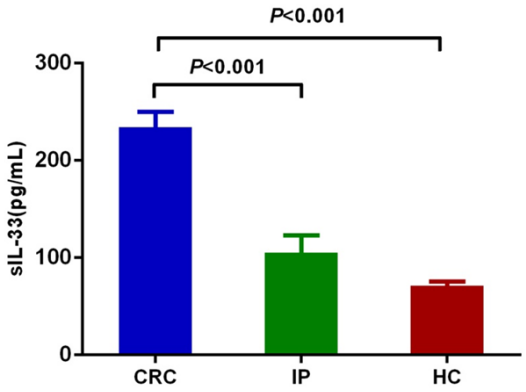

Figure 3. Serum IL-33 level in colorectal cancer and control group. Abbreviations: CRC, colorectal cancer. IP, intestinal polyp. HC, healthy control.

patients' gender, age, tumor diameter, degrees of differentiation, lymphatic metastasis, AJCC TNM staging, tumor location and histological type. As is shown in **Table 4**, serum IL-33 levels in moderate or poor differentiation CRC cases were significantly higher than that in well differentiation cases (Z = 6.25, P < 0.01). Serum IL-33 level in colon cancer cases were also significantly higher than that in rectal cancer cases (Z = 2.90, P < 0.01). Other clinical features showed no significant differences when compared with serum IL-33 levels.

Logistic regression model with IL-33 involved in for CRC diagnosis

The CRC group was set as disease group. Similarly, the intestinal polyp control group and healthy control group was set as control group. Each case in disease and control group had serum IL-33, CEA (carcinoembryonic antigen) and CA 19-9 (carbohydrate antigen 19-9)

Table 4. Serum IL-33 level in CRC and its correlation with clinical features

Clinical features	Total	sIL-33 (pg/mL)	Z	*P*
Gender				
Male	72	163.68 (114.16, 357.83)	0.09	0.93
Female	49	189.53 (103.35, 291.53)		
Age			0.15	0.88
≥ 60 yrs	76	173.94 (107.39, 293.82)		
< 60 yrs	45	165.01 (164.90, 342.08)		
Tumor diameter			0.47	0.63
≥ 5 cm	55	178.11 (105.86, 323.44)		
< 5 cm	66	165.23 (110.43, 313.32)		
Differentiation			6.25	< 0.01*
Well	68	114.64 (86.84, 196.04)		
Moderate or poor	53	278.51 (182.28, 425.88)		
Lymphatic metastasis			0.06	0.95
Yes	44	168.94 (112.61, 283.81)		
No	77	175.45 (104.46, 356.34)		
AJCC TNM staging			0.06	0.95
I/II	77	175.45 (104.46, 356.34)		
III/IV	44	168.94 (112.61, 283.81)		
Tumor location			2.90	< 0.01*
Colon	53	211.40 (135.49, 417.55)		
Rectum	68	142.05 (88.67, 249.15)		
Histological type			1.52	0.13
Ulcerative	98	183.82 (112.69, 352.03)		
Protrude	23	139.82 (91.33, 215.44)		

Notes: *statistical significance.

Table 5. Binary logistic regression model output

Variable	Alias	CR	SE	Wald	*P*
Serum IL-33	a	0.015	0.003	32.29	< 0.01
CEA	b	0.498	0.114	19.122	< 0.01
CA19-9	c	0.046	0.019	6.245	0.012
Constant	n/a	-4.01	0.53	57.357	< 0.01

Abbreviations: CR, coefficient of regression. SE, standard error. Wald, Wald chi-square value. P, *P* value. n/a, not applicable.

detected. Binary regression model method was used to generate a formula for diagnosis. The logistic regression analyze output was shown in **Table 5**. In accordance with the output, the formula was log [p (1-p)] =0.015*a+0.498*b+0.046*c-4.01. Each case had morbidity probability (p) worked out derived from the formula. The new parameter, morbidity probability, was identified as a combined biomarker integrated from three biomarkers, also well as CEA, CA19-9 and serum IL-33 alone.

Comparison of serum IL-33, CEA, CA19-9 and combination for CRC diagnosis

The receiver operating characteristic (ROC) analyze was used to compare serum IL-33, CEA, CA19-9 and combination for CRC diagnosis. As is shown in **Figure 4**, The AUC (Area Under roc Curve) of combined diagnosis was 0.9334 (95% CI: 0.9026~0.9643), higher than that of serum IL-33 (0.8446, 95% CI: 0.7938~0.8954), CEA (0.8394, 95% CI: 0.7882~0.8905), and CA19-9(0.7390, 95% CI: 0.6736~0.8043), respectively.

The cut-off values of serum IL-33 and combined diagnosis were set when maximum Youden index (sensitivity+specificity-1) was found. Therefore, the optimum cut-off value for serum IL-33 and combined diagnosis were 101.5 ng/mL and 0.52, respectively. The cut-off values of CEA and CA19-9 were set according to standard criterion, that is, 5 ng/mL and 37 ng/mL, respectively. As a consequence, the sensitivity, specificity, PPV (positive predictive value), NPV (negative predictive value) and accuracy were calculated out. As is shown in **Table 6**, CEA and CA19-9 had higher specificity and lower sensitivity for CRC diagnosis. The sensitivity of serum IL-33 was higher than CEA and CA19-9, while it had lower sensitivity than CEA and CA19-9. The combined diagnosis had maximum sensitivity and accuracy, and the specificity was at a high level.

Discussion

Cancer development is strongly influenced by innate and adaptive immunity. The immune system consists of complex structures, some of which may promote tumorigenesis, and some has inhibiting effect on tumorigenesis [6]. Interleukin-33 (IL-33), a cytokine of the IL-1

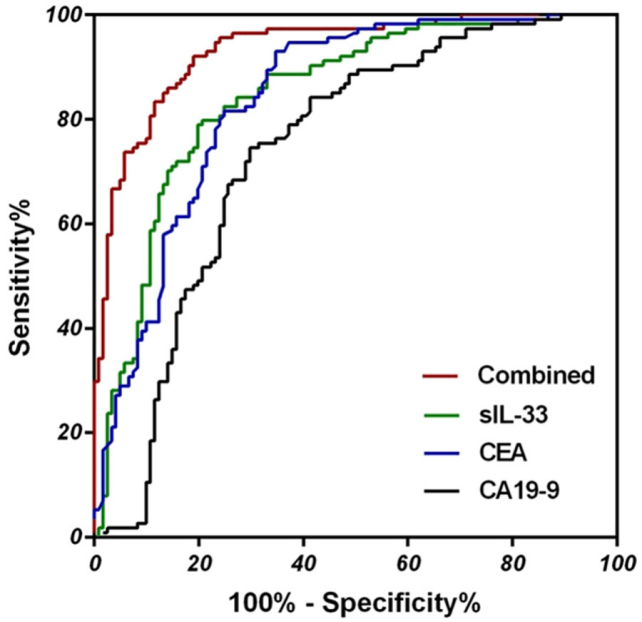

Figure 4. ROC of serum IL-33, CEA, CA19-9 and combination for CRC diagnosis.

Table 6. Comparison of different markers for CRC diagnosis

Markers	Sensitivity	Specificity	PPV	NPV	Accuracy
CEA	46.28	97.37	94.92	63.07	71.06
CA19-9	18.18	98.25	91.67	53.08	57.02
Serum IL-33	79.34	79.82	80.67	78.45	79.57
Combined	80.99	92.11	91.59	82.03	86.38

family, was identified as a legend for the ST2. The IL-33/ST2L axis stimulates the generation of cytokines and type 2 immune response [7].

Recently, several studies have found the association between expression of IL-33 and different types of solid tumors. Yang et al. demonstrated that serum concentration of IL-33 and ST2 were significantly higher in patients with breast cancer than in healthy volunteers, respectively. IL-33 and sST2 may serve as non-invasive diagnosis markers for breast cancer [8]. Kim et al. found that serum IL-33 levels are associated with progression of lung cancer. Serum IL-33 levels were significantly lower in cancer patients than normal controls, and were higher at stage I and markedly lower at stages III and IV than those of controls [9]. Ye et al. did a study suggesting that the level of serum IL-33 should be detected during the treatment of gastric cancer, particularly when using platinum-based chemotherapeutics, so that clinicians can determine the best treatment plan for different patients [10]. Schmieder et al. reported that IL-33 may act as a crucial mediator in inflammation-associated pancreatic tumorigenesis [11]. Bergis et al. found that no significant difference of serum IL-33 levels existed in hepatocellular carcinoma compared to liver cirrhosis and healthy controls. IL-33 levels did not correlate with overall survival and liver function parameters [12]. Chen et al. found that IL-33 is a potential prognostic biomarker that could be considered in therapeutic strategies for the treatment of patients with head and neck squamous cell carcinoma [13]. Zhao et al. found that IL-33 and its receptor ST2 may be a potential therapeutic target for the treatment of pain in bone cancer patients [14]. Tong found that IL-33/ST2 pathway associates with poor prognosis of epithelial ovarian cancer patients, and it promotes ovarian cancer growth and metastasis [15].

In the present study, we found that he positive expression rate of IL-33 in tumor tissues was significantly lower than that in peritumoral tissues, and the higher level of pathological grading, the lower expression of IL-33 in tumor tissues. The conclusion was similar to the study of serum IL-33 in lung cancer [9], but in the present study of serum, no similar result was found. Patients with positive IL-33 expressions have no significant different overall survival compared with those with negative IL-33 expressions in the present study, the same as the result in the study of hepatocellular carcinoma [12]. We also found that serum IL-33 levels in moderate or poor differentiation CRC cases were significantly higher than that in well differentiation cases. Serum IL-33 level in colon cancer cases was also significantly higher than that in rectal cancer cases. These findings suggested that serum IL-33 level may suggest malignancy degree and location of colorectal cancer. Finally, we established a logistic regression model involving serum IL-33 and conventional tumor markers for colorectal diagnosis. Diagnosis result analysis suggested that combination of serum IL-33, CEA and CA19-9 may improve diagnostic efficiency for colorectal

cancer. However, this finding should be verified in a large cohort of colorectal patients and in prospective randomized clinical studies. Moreover, the detailed mechanisms of IL-33 in colorectal cancer tumorigenesis and metastasis need comprehensive deeper research.

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Disclosure of conflict of interest

None.

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