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The Diagnostic Value of Serum L1CAM in Patients With Colorectal Cancer

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Abstract

Objective: Colorectal cancer is one of the most important malignant cancer in the world with high incidence and mortality. Some studies have found that the expression of low serum L1 cell adhesion molecule is associated with poor prognosis in some malignancies. It is suggested that L1 cell adhesion molecule is a candidate serum marker for certain tumors. However, the relationship between serum L1 cell adhesion molecule and colorectal cancer, especially about the diagnostic value, is rarely reported. Therefore, this study aimed to evaluate the diagnostic potential of serum L1 cell adhesion molecule in patients with colorectal cancer. **Methods:** Enzyme-linked immunosorbent assay was carried out to detect L1 cell adhesion molecule level in sera of 229 patients with colorectal cancer and 145 normal controls. Receiver operating characteristic curves were employed to calculate the accuracy of diagnosis. **Results:** The levels of serum L1 cell adhesion molecule in the colorectal cancer group were significantly lower than that in normal controls ($P < .05$). In the normal group, the area under the receiver operating characteristic curve (area under the curve) of all colorectal cancer was 0.781 (95% confidence interval: 0.734-0.828) and early-stage colorectal cancer was 0.764 (95% confidence interval: 0.705-0.823). With optimized cutoff of 17.760 ng/mL, L1 cell adhesion molecule showed certain diagnostic value with specificity of 90.3% and sensitivities of 43.2% and 36.2% in colorectal cancer and early-stage colorectal cancer, respectively. Clinical data analysis showed that the levels of L1 cell adhesion molecule were significantly correlated with gender ($P < .05$) and early and late stages ($P < .05$). Furthermore, when compared with carcinoembryonic antigen, serum L1 cell adhesion molecule had significantly improved diagnostic accuracy for both colorectal cancer and early-stage colorectal cancer. **Conclusions:** Our study demonstrated that serum L1 cell adhesion molecule might be served as a potential biomarker for the diagnosis of colorectal cancer.

Keywords

colorectal cancer, L1CAM, serum, biomarker, diagnosis

Abbreviations

AJCC, American Joint Committee on Cancer; AUC, area under the ROC curve; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; CRC, colorectal cancer; ELISA, enzyme-linked immunosorbent assay; ESCC, esophageal squamous cell cancer; L1CAM, L1 cell adhesion molecule; ROC, receiver operating characteristic; SD, standard deviation.

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Introduction

Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies. It is the third leading incident cause of cancer and the second leading cause of cancer-related death in the world. It is estimated that 1.8 million new CRC cases and 881 000 deaths occurred in 2018, accounting for about 1 in 10 cancer cases and deaths.[1] In the past decades, with the changes in people's lifestyles and dietary habits, the incidence and mortality of CRC in China have risen rapidly.[1-3] Most patients with CRC are asymptomatic early, and once clinical symptoms appear, the patient may be in advanced stage of cancer, or even accompanied by distant metastasis.[4] The 5-year survival rate of patients with distant metastasis is very low; even after surgery and comprehensive treatments, it is still less than 20%.[4,5] It is widely believed that CRC is curable at the early stage, as many other cancers.[6] Thus, early detection of CRC is the key to improve survival rates, and an effective screening program is needed.

Currently, colonoscopy is the most common and effective method for the diagnosis of CRC.[7] But it is an invasive method, which often causes discomfort to patients and is not suitable for screening early CRC.[8] In addition, some other CRC screening tests including fecal occult blood testing, stool DNA test, carcinoembryonic antigen (CEA), or a combination assay of CEA and carbohydrate antigen 19-9 (CA19-9) were carried out to reduce the incidence and mortality of CRC.[9,10] However, because of the invasiveness, low sensitivity, or high cost, none of these methods has been identified as a recognized screening tool.[9-11] Therefore, finding noninvasive and reliable tools to identify patients with early CRC is the key to effective treatment and improvement in the prognosis of patients with CRC.

The L1 cell adhesion molecule (L1CAM) belongs to the immunoglobulin superfamily and was initially identified in the nervous system.[12] Current studies have shown that L1CAM, as a structural molecule on the cell membrane of neurons, is not only involved in routine transmembrane signal transduction but also closely related to the adhesion, recognition, and migration of neurons.[13,14] Some studies found that high L1CAM expression is associated with poor prognosis in breast cancer,[15] glioma,[16] melanoma,[17] renal cell carcinomas,[18] non-small cell lung cancer,[19] gastric cancer,[20] uterine and ovarian cancers,[21] and other less common types of cancer. These indicate that L1CAM is a candidate serum biomarker for some tumors. In our previous studies, serum L1CAM and circulating autoantibodies against L1CAM levels were measured by enzyme-linked immunosorbent assay (ELISA). The results showed that L1CAM and L1CAM autoantibodies could be used as potential biomarkers for early detection of ESCC.[22,23] In addition, upregulation of L1CAM in CRC tissues and the correlation between L1CAM expression and poor prognosis of patients with CRC have been reported.[24,25] However, use of serum L1CAM as a clinical biomarker in patients with CRC has not yet been examined. Therefore, in this study, we aimed to evaluate whether L1CAM could be detected and serve as a diagnostic biomarker in patients with CRC.

Materials and Methods

Study Samples

In this study, 229 serum samples from patients with CRC and 145 serum samples from normal controls were selected. The serum samples of 229 patients with CRC were collected from the Cancer Hospital of Shantou University Medical College and the First Affiliated Hospital of Shantou University Medical College, from September 2013 to October 2018. A total of 145 normal controls were selected from the Cancer Hospital of Sun Yat-sen University Medical College and the First Affiliated Hospital of Shantou University Medical College, from February 2017 to October 2018. The cancer group were all newly diagnosed patients without any anticancer treatment before blood collection, and the follow-up data were completed. The normal controls were qualified blood donors and all of them have no evidence of cancer. Peripheral blood samples of patients and controls were coagulated at room temperature for 30 minutes before centrifuged at 1250*g* for 5 minutes and then stored at -80°C until the experiment started.

The clinicopathological data of all patients with CRC were recorded, including age, sex, depth of tumor invasion, lymph node metastasis, distant metastasis, and Tumor Node Metastasis (TNM) stage (according to the eighth edition of the American Joint Committee on Cancer [AJCC] Cancer Staging Manual[26]). In the study, we classified tumors with AJCC stage 0 + I + II as early-stage CRC. The study was approved by the Ethics Committee of the Cancer Hospital of Shantou University Medical College (2015042419), the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College (2018064), and the Ethics Committee of the Cancer Hospital of Sun Yat-sen University Medical College (GZR2015-015), and informed consents were obtained from all included participants. All work was complied with the principles of the Helsinki Declaration.

Analysis of Serum L1CAM and CEA Levels

Levels of serum L1CAM were measured by ELISA according to our previous publications.[22,23] The procedure was carried out according to the instructions of the ELISA kit (Sino Biological Inc, cat.no. SEK10140, Beijing, China). Briefly, 96-well microplates (Biohaotian, cat. no. HT081, Jiangsu, China) were coated with 100 μL diluted capture antibody (2 μg/mL) per well and incubated overnight at 4°C. The plates were washed 3 times by microplate washer (Thermo Fisher Scientific, Boston, USA) and then blocked by adding 300 μL of blocking buffer and incubated for 1 hour at room temperature. After removing the liquid and washing conducted for 3 times, 100 μL of serum samples (a 200-fold dilution) and standards were added per well and incubated at room temperature for 2 hours. The concentrations of the L1CAM standard curve were 0, 47, 94, 188, 375, 750, 1500, and 3000 pg/mL, respectively. Then, plates were washed 3 times, 100 μL of detection antibody (0.5 μg/mL) was added per well and incubated at room temperature for 1 hour. Followed by 5 washes, 200 μL

substrate solution was added to each well and then incubated for 20 minutes at room temperature. Optical density values were read at 450 and 570 nm wavelengths within 5 minutes after adding stop solution (Thermo Fisher Scientific, Boston, USA). The serum L1CAM concentrations were obtained by plotting a standard curve with a 4-parameter logistic curve manner and multiplied by the dilution factor. The serum levels of CEA were quantified using a UniCel DXi 800 Analyzer (Shanghai, China). According to the manufacturer's instructions, the cutoff value for normal CEA is less than 9.7 ng/mL. All measurements including samples and standards were done in duplicate.

Statistical Analysis

Statistical analysis was performed using SPSS version 19.0 software, GraphPad Prism version 7.0 software, and Microsoft Excel. We used a nonparametric Mann-Whitney *U* test to analyze the difference in serum L1CAM levels between CRC and control groups. All data are expressed as means ± standard deviations (SDs). The receiver operating characteristic (ROC) curves were used to evaluate the diagnostic value of serum L1CAM in the identification of patients with and without CRC. The ROC analysis was performed to assess the optimum cutoff value, sensitivity, specificity, and area under the ROC curve (AUC) with the 95% confidence interval (CI). As previously described, when the specificity was >90%, we chose the cutoff value by maximizing the sensitivity of curvilinear coordinates and minimizing the distance between the corresponding points in the ROC curve (CRC group and normal control) to the upper left corner.[22,23] The specificity >90% was selected to produce an economical, feasible, and suitable tests for early detection purposes.[27] By using these optimal cutoff values, positive predictive values, negative predictive values, positive likelihood ratio, and negative likelihood ratio were calculated. To explore the relationship between serum L1CAM level and clinicopathological factors, χ^2 tests were used to analyze the differences among groups. All tests were 2 tailed and a *P* value less than .05 was considered statistically significant.

Results

Serum Level of L1CAM Decreased in Patients With CRC

In total, 374 participants were recruited, 229 patients with CRC and 145 normal controls. There were 133 males and 96 females in the patient group, ranging in age from 26 to 85 years (mean, 60 years). The control group was consisted of 113 males and 32 females aged between 29 and 86 years (mean, 58 years; Table 1). As shown in Table 2, the levels of L1CAM (mean ± SD) were 24.028 ± 17.255 ng/mL in CRC sera, 35.455 ± 17.558 ng/mL in early-stage CRC sera, and 44.010 ± 23.055 ng/mL in control sera, respectively. The distribution level of L1CAM in different clinical stages of CRC is shown in Supplementary Table 1. The ELISA results showed that serum L1CAM in patients with CRC and early CRC were significantly lower than that in normal controls (Figure 1A). Our data demonstrated that serum levels of L1CAM decrease in patients with CRC.

Table 1. Participant Information and Clinicopathological Characteristics.

Group	Patients With CRC (n = 229)	Normal Controls (n = 145)
Age (years)		
Mean ± SD	60 ± 12	58 ± 12
Range	26-85	29-86
Gender		
Male	133	113
Female	96	32
Depth of tumor invasion		
T1	6	
T2	32	
T3	51	
T4	139	
Unknown	1	
Lymph node metastasis		
N0	119	
N1	69	
N2	39	
Unknown	2	
Distant metastasis		
Yes	20	
No	208	
Unknown	1	
TNM stage		
I	27	
II	89	
III	90	
IV	22	
Unknown	1	

Abbreviations: CRC, colorectal cancer; SD, standard deviation; TNM, tumor node metastasis.

Table 2. Comparison Between 3 Groups.

		Serum L1CAM Expression	
	n	Mean ± SD	*P* Value[a]
CRC	229	24.028 ± 17.255	<.001
Early-stage CRC (0 + I + II)	116	35.455 ± 17.558	<.001
Normal controls	145	44.010 ± 23.055	

Abbreviations: CRC, colorectal cancer; L1CAM, L1 cell adhesion molecule; SD, standard deviation.
[a]Compared with normal controls.

Evaluation of Serum L1CAM as a Potential Diagnostic Biomarker for CRC

We performed an ROC analysis to assess the ability of L1CAM to distinguish patients with CRC from healthy controls. The ROC curve analysis showed that the optimized cutoff value for L1CAM was 17.760 ng/mL, which had an AUC of 0.781 (95%

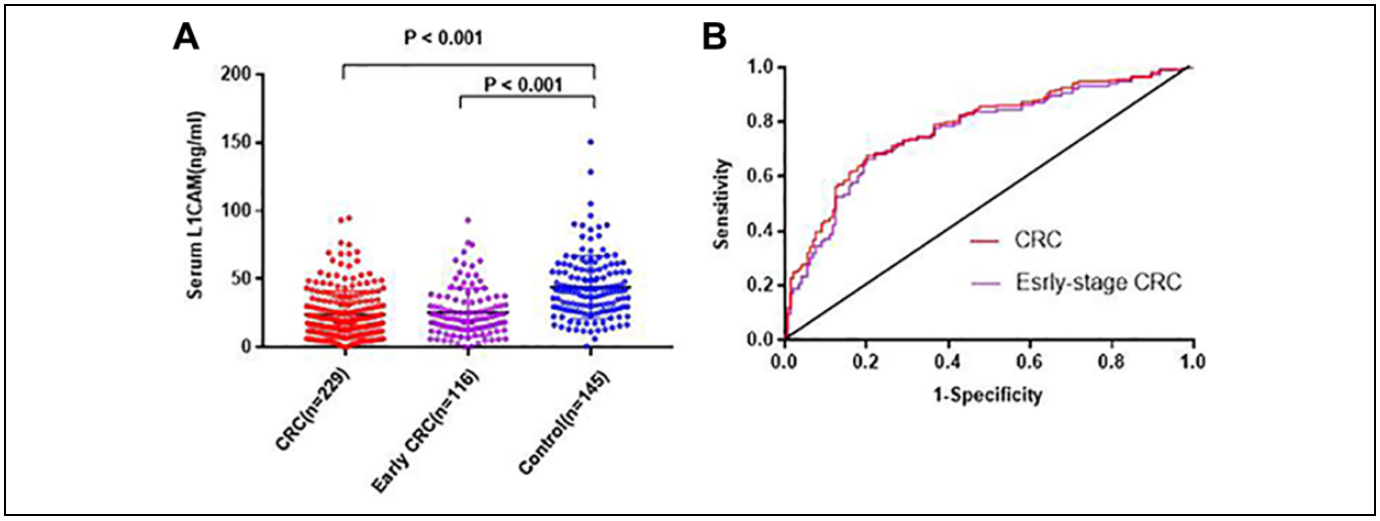

Figure 1. Patients with CRC have decreased levels of serum L1CAM and ROC curve analysis of the diagnostic performance of L1CAM. A, Serum levels of L1CAM were determined by ELISA in patients with CRC, patients with early-stage CRC, and normal controls. B, The ROC curves for serum L1CAM for patients with CRC, early-stage CRC, versus normal controls. Black horizontal lines are means, and error bars are SEs. The area under the block line is 0.5, for reference. CRC indicates colorectal cancer; ELISA, enzyme-linked immunosorbent assay; L1CAM, L1 cell adhesion molecule; ROC, receiver operating characteristic curve; SE, standard error.

Table 3. Results for Measurement of L1CAM in the Diagnosis of CRC.

Group	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR
L1CAM							
CRC vs NC	0.781 (0.734-0.828)	43.2 (36.8-49.9)	90.3 (84.0-94.4)	87.6	50.2	4.48	0.63
Early-stage CRC vs NC	0.764 (0.705-0.823)	36.2 (27.6-45.7)	90.3 (84.0-94.4)	75.0	63.9	3.75	0.71

Abbreviations: AUC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; CRC, colorectal cancer; L1CAM, L1 cell adhesion molecule; NC, normal controls; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.

CI: 0.734-0.828), a sensitivity of 43.2% (95% CI: 36.8%-49.9%), and a specificity of 90.3% (95% CI: 84.0%-94.4%) for distinguishing CRC from controls (Figure 1B and Table 3). In the early-stage CRC, measurement of L1CAM provided an AUC of 0.764 (95% CI: 0.705-0.823), 36.2% (95% CI: 27.6%-45.7%) sensitivity, and 90.3% (95% CI: 84.0%-94.4%) specificity (Figure 1B and Table 3). Table 3 shows the predicted value and likelihood ratio of serum L1CAM to improve the clinical interpretation in the diagnosis of CRC.

Relationship of Serum L1CAM and Clinicopathological Status in Patients With CRC

We assessed the relationship between serum L1CAM and clinicopathological status of patients with CRC by comparing serum L1CAM levels in all 229 patients with CRC. Table 4 shows the correlation between L1CAM level and clinicopathological characteristics. In our experiment, serum L1CAM levels were not associated with age, depth of tumor invasion, lymph node metastasis, and distant metastasis, but decreased L1CAM levels were associated with gender ($P < .05$) and advanced TNM stages ($P < .05$).

Diagnostic Capacity of CEA and a Combination of L1CAM and CEA

A total of 97 serum samples from the First Affiliated Hospital of Shantou University Medical College were selected to analyze the diagnostic effect of L1CAM and CEA. Patient and normal control information and clinicopathological characteristics are shown in Supplementary Table 2. Detection of L1CAM provided a sensitivity of 50.5%, a specificity of 91.3%, and an AUC of 0.876 (95% CI: 0.821-0.930) in diagnosing CRC (Figure 2A, Table 5). The AUC for CEA in distinguishing between patients with CRC from normal controls was 0.746 (95% CI: 0.675-0.817); use of the typical cutoff value of 9.7 ng/mL led to a sensitivity of 21.6% and a specificity of 100% (Figure 2B, Table 5). When combined with L1CAM and CEA, we acquired an AUC of 0.926 (95% CI: 0.888-0.965) with a sensitivity/specificity of 77.3%/91.3% (Figure 2C, Table 5). When using the same cutoff value to evaluate the diagnostic ability of L1CAM and CEA in early-stage CRC, we observed similar results as in all-stage CRC (Figure 2, Table 5).

Table 4. Relationship Between Positive Rates of L1CAM and Clinicopathologic Features in Patients With CRC.

	n	Positive	%	χ^2	*P* Value
Patient age					
<60	94	43	45.7	0.567	.452
≥60	135	55	40.7		
Gender					
Male	133	47	35.3	7.205	.007
Female	96	51	53.1		
Depth of tumor invasion					
T1	6	2	33.3	3.658	.454
T2	32	10	31.3		
T3	51	21	41.2		
T4	139	65	46.8		
Unknown	1	-	-		
Lymph node metastasis					
N0	119	43	36.1	7.947	.094
N1	69	38	55.1		
N2	39	16	41.0		
Unknown	2	1	50.0		
Distant metastasis					
M0	208	88	42.3	1.192	.551
M1	20	10	50.0		
Unknown	1	-	-		
TNM stage					
Early stage (I + II)	117	42	35.9	4.649	.031
Advanced stage (III + IV)	112	56	50.0		

Abbreviations: CRC, colorectal cancer; L1CAM, L1 cell adhesion molecule.

Discussion

Studies have reported that CRC outcomes and prognosis are related to clinical stage and metastasis of the tumor. The 5-year survival rate of most patients with early CRC is over 90%,[4,9,28] the 5-year survival rate of patients with locally advanced CRC is 70%,[4,28] and the 5-year survival rate of patients with distant metastasis is less than 20%.[5,9] As far as we know, due to early detections and treatments, the mortality rate of CRC is declining in some developed countries.[29] Therefore, early detection of CRC is of great significance, timely treatment, to avoid the occurrence of metastatic diseases. In recent years, the research on early diagnostic markers of CRC has been one of the hotspots at home and abroad. Biochemical substances produced or secreted by malignant tumor cells during the process of proliferation are tumor markers, and their changes in blood concentration may indirectly reflect the nature and structure of tumor tissues and the function and differentiation of tumor cells.[30] At present, CEA and CA19-9 are the most widely studied CRC tumor markers.[9,11,31] However, the low sensitivities or specificities of CEA and CA19-9 in CRC screening are still clinical problems.[9,11,31,32] Therefore, it is necessary to find new biomarkers with high sensitivity and specificity for early screening of CRC. Our research showed that L1CAM may be one of the potential candidates.

L1 cell adhesion molecule, also known as CD171, is a class of transmembrane proteins that mediate cell-to-cell and extracellular matrix adhesion.[12-14] The exterior part of the cell consists of 6 immunoglobulin domains and 5 fibronectin repeats (type III), which are connected to a small intracellular domain by a transmembrane helix.[12,33] A large number of studies have found that L1CAM is expressed in many human cancers and is usually associated with poor prognosis.[15-21] In addition, recent studies have shown that L1CAM can be detected in serum and has prognostic values in patients with ESCC[22] and gastrointestinal stromal tumors.[34] At present, most studies on the expression of L1CAM in CRC have been carried out at the level of RNA and immunohistochemistry.[24,25] In order to evaluate the role of L1CAM as a peripheral marker, we examined the level of L1CAM in serum of patients with CRC and normal controls. Our study found that serum L1CAM levels in patients with early CRC and CRC were significantly lower than those in normal controls ($P < .05$). And this is similar to the data we published in the ESCC,[22] which provided evidence that serum L1CAM may be a biomarker for the diagnosis of CRC.

In the present study, serum L1CAM performed a diagnostic value in CRC with AUC of 0.781, specificity of 90.3%, and sensitivity of 43.2%. Moreover, we noted similar diagnostic performance of serum L1CAM in patients with early-stage CRC. As for the relationship between serum L1CAM and the clinical data of CRC, we found that the level of serum L1CAM was associated with more advanced TNM staging. However, previous reports indicate that high expression of L1CAM in CRC tissues is associated with more advanced TNM staging.[24,25] We believe that this contradiction may be due to different expression patterns of L1CAM in serum and pathological tissues.[22] In clinical practice, the staging of tumor necrosis mainly depends on the postoperative pathological analysis of tissue specimens.[35] However, due to its invasive nature, it is not suitable for large-scale clinical screening. Therefore, serum L1CAM may be more acceptable in certain clinical settings. Considering the important role of TNM stage, we believe that serum L1CAM may have potential as an additional biomarker for CRC prognosis assessment. In addition, due to the age mismatch between the normal control group and the patient with CRC, the corresponding age can be further studied. But as the result that there is no significant relationship between L1CAM and age, the bias of age in 2 groups could be decreased. In fact, our main objective in this study is to assess the ability of L1CAM to detect early CRC. Although the sensitivity and specificity need to be improved, to our knowledge, this is the first report to address the diagnostic value of serum L1CAM for early-stage CRC. We believe that if large-sample and multicenter early cases are used, our study will significantly improve the ability of serum L1CAM to treat early CRC.

Next, we analyzed the diagnostic effect of L1CAM and CEA in 97 serum samples. It was found that the AUC for L1CAM (0.876) was higher than CEA (0.746), indicating that L1CAM performs better than CEA in discriminating patients with CRC from healthy controls. As for the early-stage CRC, the positive frequency of L1CAM was 50.5% (95% CI: 40.2%-60.7%) and that of CEA was 24.6% (95% CI: 14.5%-38.0%). Thus, L1CAM improves the diagnostic performance in

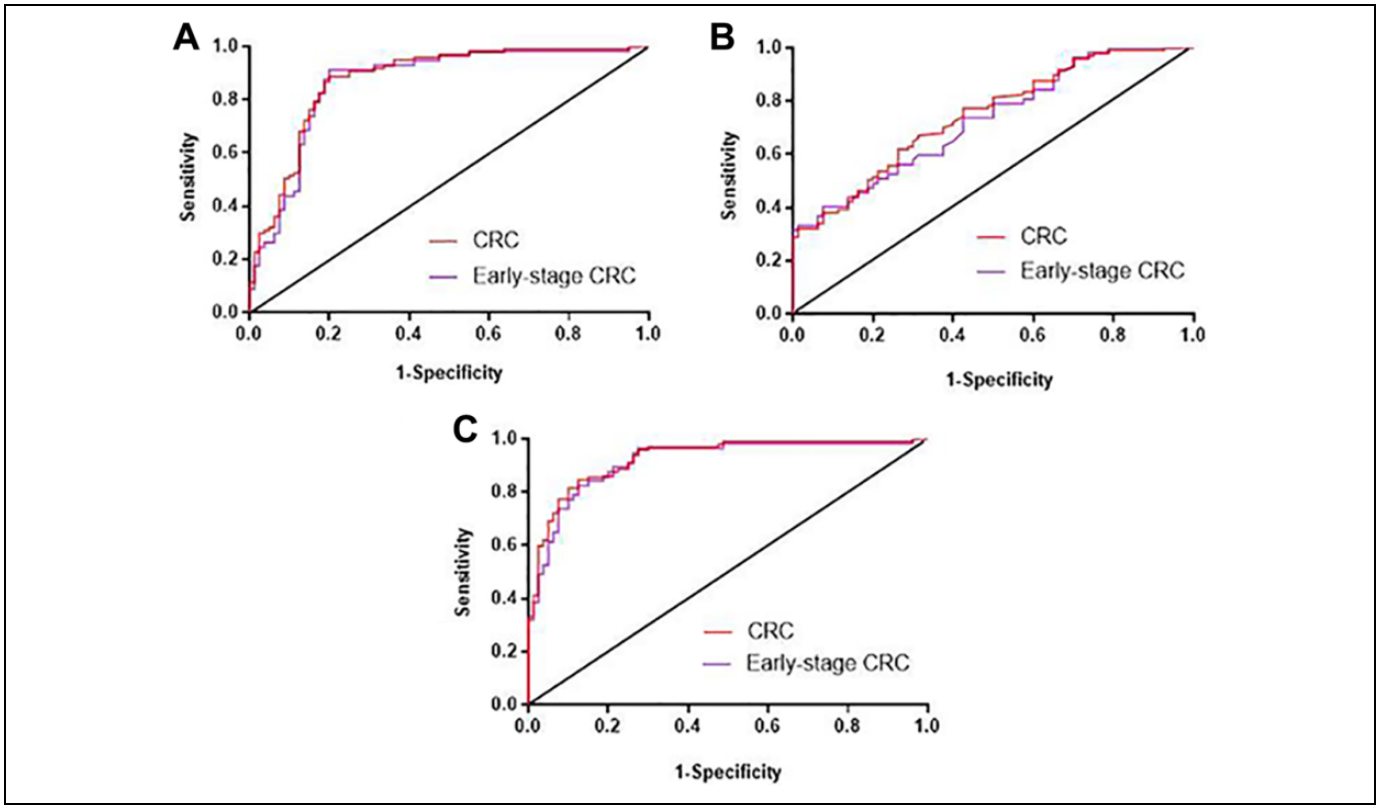

Figure 2. The ROC curve analysis in the diagnosis of CRC and early-stage CRC. Two groups versus NC group are in different colors. A, The ROC curves for serum L1CAM for patients with CRC, early-stage CRC, versus normal controls. B, The ROC curves for serum CEA for patients with CRC, early-stage CRC, versus normal controls. C, The ROC curves of serum L1CAM and CEA in patients with CRC and early-stage CRC were compared with those in the NC group. The area under the block line is 0.5, for reference. CEA indicates carcinoembryonic antigen; CRC, colorectal cancer; L1CAM, L1 cell adhesion molecule; NC, normal control; ROC, receiver operating characteristic curve; SE, standard error.

Table 5. The ROC Curve Assay of L1CAM, CEA, and a Combination of L1CAM and CEA.

Variables	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
CRC vs NC			
L1CAM	0.876 (0.821-0.930)	50.5 (40.2-60.7)	91.3 (82.3-96.1)
CEA	0.746 (0.675-0.817)	21.6 (14.2-31.4)	100 (94.3-100)
L1CAM + CEA	0.926 (0.888-0.965)	77.3 (67.5-85.0)	91.3 (82.3-96.1)
Early-stage CRC vs NC			
L1CAM	0.865 (0.801-0.929)	43.9 (31.0-57.6)	91.3 (82.3-96.1)
CEA	0.729 (0.645-0.813)	24.6 (14.5-38.0)	100 (94.3-100)
L1CAM + CEA	0.915 (0.866-0.965)	73.7 (60.1-84.1)	91.3 (82.3-96.1)

Abbreviations: AUC, area under the ROC curve; 95% CI, 95% confidence interval; CEA, carcinoembryonic antigen; CRC, colorectal cancer; L1CAM, L1 cell adhesion molecule; NC, normal control; ROC, receiver operating characteristic.

early-stage CRC samples, compared with CEA. Moreover, studies have reported that in stage 0 and stage I cancers, CEA positive frequencies are only 16.7% and 13.2%, respectively.[36] This result also shows that the early diagnosis of CRC by CEA is not satisfactory because it increases significantly in the late stage of cancer.[32,36] Although CEA has good specificity for early CRC, when screening for large populations with low CRC prevalence, due to low sensitivity and large population, even if the false-positive rate is very low, many false-positive results will be obtained. Therefore, L1CAM may be considered as a potential serum marker for early clinical diagnosis of CRC. However, the sensitivity of diagnosing CRC with L1CAM alone does not seem to meet the clinical requirements, which will prevent some asymptomatic early patients from diagnosing CRC in time. Therefore, if L1CAM is used as a screening tool for CRC, especially for early-stage patients in a general population, further diagnosis should involve additional imaging tests, such as gastroscopy. In recent years, convincing evidence has emerged that effective and accurate detection of cancer, especially for early cancer, may depend on the

combination of many biomarkers produced by different mechanisms, which have higher sensitivity and specificity than single biomarker.[31,36,37] In our experiment, combined with L1CAM and CEA, the sensitivity increased from 50.5% to 77.3%. It has also been reported that the combination of CEA and CA19-9 can improve the diagnostic rate of CRC and increase its sensitivity from 47.8% to 71.7%.[31] Therefore, we hope that L1CAM can be combined with some commonly used CRC tumor markers (such as CEA, carbohydrate antigen 724, CA199, cytokeratin19 fragment 21-1) to diagnose early CRC, so as to improve the positive detection rate of early CRC.

Conclusion

In conclusion, the current study is the first to show a significant decrease in serum L1CAM levels in patients with CRC. Our results suggested that L1CAM should be considered as a potential serum biomarker for the diagnosis of CRC, although these results must be confirmed in larger samples and different populations.

Authors' Note

Ling-Yu Chu and Dong-Ming Guo contributed equally to this work. The study was approved by the Ethics Committee of the Cancer Hospital of Shantou University Medical College (2015042419) and the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College (2018064), and informed consents were obtained from all included participants.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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