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The risk factors for bone metastases in patients with colorectal cancer

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Abstract

This retrospective analysis aim to evaluate the potential risk factors for bone metastases (BM) in patients who were diagnosed with colorectal cancer (CRC).

A total of 2790 patients diagnosed with CRC between January 2006 and December 2016 were collected in this study. All patients were divided into 2 groups, BM and no BM. The associations between biomarkers (including age, gender, histopathological types, alkaline phosphatase (ALP), carcinoembryonic antigen (CEA), cancer antigen 125, and so on), and BM in patients with CRC were analyzed. All the analyses were conducted by SPSS software (version 22.0, SPSS, Chicago, IL).

Of all patients, 74 (2.7%) were identified with BM. The level of serum ALP, CEA, and cancer antigen 125 in patients with BM were obviously higher than those without BM ($P < .001$, $P = .005$, and $P < .001$). And the cut-off values of ALP, CEA, and cancer antigen 125 were 85.5 U/L, 6.9 mmol/L, and 16.8 mmol/L, respectively.

ALP, CEA, and cancer antigen 125 were identified as the independent risk factors for BM in patients with CRC.

Abbreviations: ALP = alkaline phosphatase, AUC = area under the curve, BM = bone metastases, CA199 = cancer antigen 125 (CA125) and cancer antigen 199, CEA = carcinoembryonic antigen, CRC = colorectal cancer, ROC = receiver operating characteristic.

Keywords: bone metastases (BM), colorectal cancer (CRC), risk factors

1. Introduction

Colorectal cancer (CRC) is a commonly malignant tumors and is the main cause of cancer-related death in patients,[1–3] with approximately 1.2 million new cases occurred each year.[4] So far, surgery remained the most important option for treating CRC, but 30% of patients still developed metastases.[5] It was well know that liver and lung were the most common sites of distant metastases in CRC. But bone is also one of the commonly distant metastasis locations.[5–8] Although the median survival of patients with CRC was significantly improved, the risk of bone metastases (BM) was also increased. In addition, patients with BM will suffer a series of complications and skeletal-related event (SRE) due to bone destruction such as pain, pathological fractures, spinal cord compression, and hypercalcemia,[6,9,10] which would decrease the quality of patients' life.[8,9] Although imaging study is still the primary method for diagnosing BM, it could not provide enough information for early diagnosis.[11] Thus, it is necessary to find a way to detect BM in patients with CRC for early diagnosing and treatment. The purpose of this study was to investigate the association between clinical parameters and BM, and to identify the risk factors for early detecting BM from CRC.

2. Materials and methods

2.1. Patient selection

This study was approved by the ethics committee of the First Affiliated Hospital of Nanchang University. A retrospective study was conducted and patients newly diagnosed with CRC between January 2006 and December 2016 were included in this study. All these diagnoses were confirmed by histopathological examination. And the diagnosing of patients with BM mainly relied on imaging studies, including computed tomography (CT) scan, magnetic resonance imaging (MRI), and bone scan. Patients who suffered from primary tumor other than CRC at the same time were excluded from this study.

2.2. Date collection

In this retrospective study, the demographic characteristics of patients with CRC were collected, such as the age, gender, histopathological types, the location of the original tumor (colon and rectal), serum level of calcium, hemoglobin, alkaline phosphatase (ALP), carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), and cancer antigen 199 (CA199) at the time of primary diagnosis. The associations between biomarkers and BM in patients with CRC were analyzed.

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2.3. Statistical analysis

All the analyses were conducted by SPSS software (version 22.0, SPSS, Chicago, IL). The continuous variables in this study were expressed as mean ± standard deviation. Patients with CRC were divided into 2 groups: bone metastasis (BM) and none bone metastasis (NBM). And Chi-square test, Fisher exact test and Student *t* test were used to determine the differences between the 2 groups. Then, the independent risk factors for bone metastasis in patients with CRC were identified by binary logistic regression analysis. In additions, receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) was calculated, which was used to assess the accuracy of predicting the risk factors for BM. A value of *P* less than .05 was defined as statistically significant.

3. Results

3.1. Patient demographics

In this study, a total of 2790 patients diagnosed with CRC were included in it. Of these patients, 1655 (59.3%) were male and 1135 (40.7%) were female, with an average age of 58 years (ranged from 15 to 95 years). Table 1 demonstrates the demographic characteristics of patients with CRC. Among these patients, rectal cancer accounted for 52.33%, colon cancer account for 47.63%, and only 0.01% of them identified with both rectal and colon cancer. The main histopathological type of these patients was adenocarcinoma (86.49%). Other histopathological types included mucinous adenocarcinoma (8.35%), signet ring cell carcinoma (0.75%), neuroendocrine cancer (0.25%), and so on.

3.2. Distribution of bone metastases in patients with CRC

The distribution of BM in CRC patients is described in Table 2. Seventy-four patients were identified with BM, and 43 (58.11%) were male and 31 (41.89%) were female. Of these patients, the most common histopathological type was adenocarcinoma, which accounted for 87.84%. For the site of bone metastasis, the most common one was the spine (62.16%), followed by pelvis (55.4%) and ribs (12.16%). According to the number of BM sites, patients with BM can be divided into 3 subgroups: metastasis to 1 site (67.57%), metastasis to 2 sites (25.67%), and metastasis to 3 and more sites (6.76%).

Table 1

Demographic characteristics of patients with colorectal cancer.

Patient characteristics	Number of patients (%) (N = 2790)
Primary site	
Rectum	1460 (52.33)
Colon	1329 (47.63)
Colorectal	1 (0.04)
Age	58.11 ± 13.30
Gender	
Male	1655 (59.3)
Female	1135 (40.7)
Histopathological type, n (%)	
Neuroendocrine cell carcinoma	7 (0.25)
Signet ring cell carcinoma	21 (0.75)
Mucinous adenocarcinoma	233 (8.35)
Adenocarcinoma	2433 (87.20)
Other	96 (3.44)

Table 2

The distribution of bone metastases in patients with colorectal cancer.

Patient characteristics	Patients, n (%) (N = 74)
Site of bone metastases	
Spine	46 (62.16)
Cervical	5 (6.76)
Thoracic	20 (27.03)
Lumbar	21 (28.38)
Ribs	9 (12.16)
Femur	2 (2.70)
Skull	3 (4.05)
Sternum	2 (2.70)
Pelvis	41 (55.40)
Sacroiliac	36 (48.65)
Pubic	3 (4.05)
Coccyx	2 (2.70)
Scapula	3 (4.05)
Clavicle	3 (4.05)
Number of metastatic sites (n)	
One site	50 (67.57)
Two sites	19 (25.67)
Three and more sites	5 (6.76)
Histopathological type, n (%)	
Neuroendocrine cell carcinoma	1 (1.35)
Signet ring cell carcinoma	1 (1.35)
Mucinous adenocarcinoma	4 (5.41)
Adenocarcinoma	65 (87.84)
Other	3 (4.05)
Gender	
Male	43 (58.11)
Female	31 (41.89)

3.3. Risk factors for bone metastasis in patients with colorectal cancer

In order to find out the risk factors for bone metastasis in patients with CRC, comparison was conducted for different variables between patients in bone metastasis and none bone metastasis groups (Table 3). For gender and tumor histopathological types,

Table 3

The association between different clinical factors and bone metastases.

Factors	BM	NBM	P
Age	57.62 ± 14.61	58.12 ± 13.27	.751
ALP	141.12 ± 120.73	77.80 ± 39.80	<.001
CEA	113.29 ± 269.36	22.93 ± 102.60	.005
CA125	48.51 ± 63.40	19.69 ± 31.64	<.001
CA199	261.41 ± 765.91	56.94 ± 250.26	.031
HB	113.93 ± 22.25	117.13 ± 23.49	.250
Calcium	2.27 ± 0.18	2.37 ± 2.87	.762
Gender	74	2716	.830
Male	43	1612	
Female	31	1104	
Histopathological types	74	2716	.203
Neuroendocrine cell carcinoma	1	6	
Signet ring cell carcinoma	1	20	
Mucinous adenocarcinoma	4	229	
Adenocarcinoma	65	2368	
Other	3	93	

ALP = alkaline phosphatase, BM = bone metastasis, Ca = calcium, CA125 = cancer antigen 125, CA199 = cancer antigen 199, CEA = carcinoembryonic antigen, HB = hemoglobin, NBM = none bone metastasis.

Table 4

Binary logistic regression model analyze the risk factors for bone metastases from colorectal cancer.

Factors	β	OR	OR (95% CI)	P
ALP	0.007	1.007	1.004–1.010	<.001
CEA	0.001	1.001	1.000–1.002	.016
CA199	0.000	1.000	0.999–1.001	.836
CA125	0.008	1.008	1.004–1.012	<.001
HB	0.000	1.000	0.989–1.010	.941

β = coefficient of regression, ALP = alkaline phosphatase, CA125 = cancer antigen 125, CA199 = cancer antigen 199, CEA = carcinoembryonic antigen, CI = confidence interval, HB = hemoglobin, OR = odds ratio.

there were no statistically significant differences between the 2 groups ($P = .830$ and $P = .203$). Also, no significant differences were found for serum calcium and hemoglobin between patients with and without BM ($P > .05$, respectively). However, patients with BM had higher concentrations of ALP, CEA, CA199, and CA125 than those without BM ($P < .001$, $P = .00$, $P < 0.001$, and $P = .031$, respectively). Binary logistic regression analysis indicated that ALP (OR = 1.007, $P < .001$), CEA (OR = 1.001, $P = .016$), and CA125 (OR = 1.008, $P < .001$) were identified to be the independent risk factors for bone metastasis in CRC (Table 4).

3.4. The cut-off values, sensitivities, and specificities of risk factors for predicting bone metastases

Figure 1 and Table 5 show the accuracy, sensitivity, and specificity of the single-factor and multifactor for predicting the risk of developing BM in patients with CRC. It was found that ALP had the highest diagnostic accuracy for predicting the risk of BM (AUC = 0.829, $P < .001$), with a sensitivity and specificity of
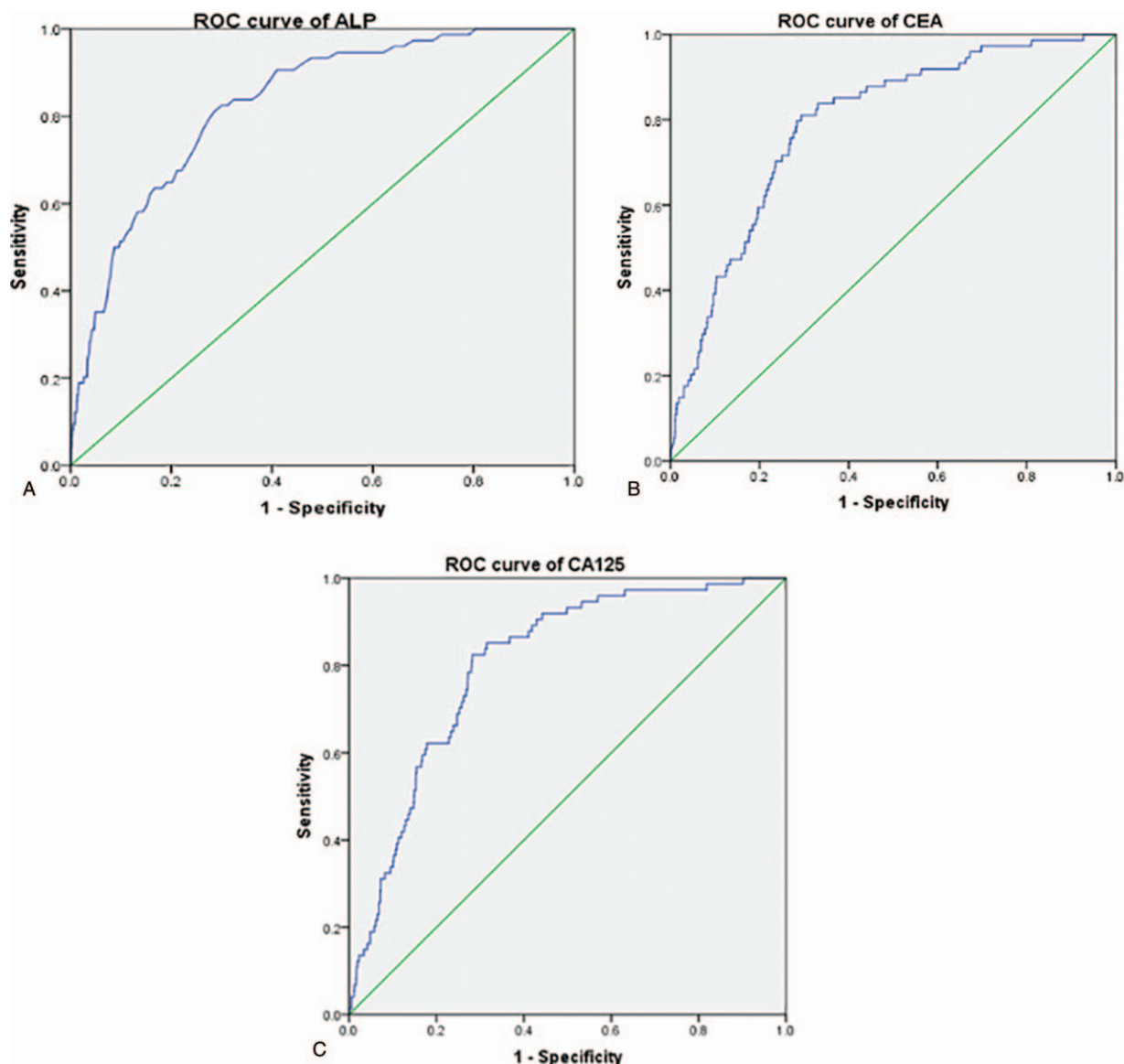

Figure 1. The receiver operating characteristics (ROC) curves of single risk factor for diagnosing bone metastases in patients with colorectal cancer. (A) The ROC of ALP. (B) The ROC of CEA. (C) The ROC of CA125.

Table 5

The cutoff value, sensitivity, and specificity of ALP, CEA, and CA125 for diagnosing bone metastasis.

Factors	Cutoff value	Sensitivity (%)	Specificity (%)	AUC	95% CI	P
ALP	85.5 U/L	81.1	71.5	0.829	0.786–0.871	<.001
CEA	6.9 mmol/L	81.1	70.6	0.791	0.743–0.838	<.001
CA125	16.8 mmol/L	82.4	71.8	0.804	0.761–0.846	<.001
CEA+ALP		86.6	69.5	0.845	0.803–0.887	<.001
CEA+CA125		86.5	68.9	0.830	0.790–0.869	<.001
ALP+CA125		87.8	71	0.864	0.833–0.895	<.001
CEA+CA125+ALP		85.1	76.6	0.874	0.844–0.904	<.001

ALP = alkaline phosphatase, AUC = area under curve, CA125 = cancer antigen 125, CEA = carcinoembryonic antigen, CI = confidence interval.

81.1% and 71.5%, respectively. And the cut-off values of ALP, CEA, and CA125 were 85.5 U/L, 6.9 mmol/L, and 16.8 mmol/L, respectively.

In combination with ALP, CEA, and CA125, it had the highest diagnostic value for identifying BM in patients with CRC (AUC = 0.874, P<.001) (Fig. 2).
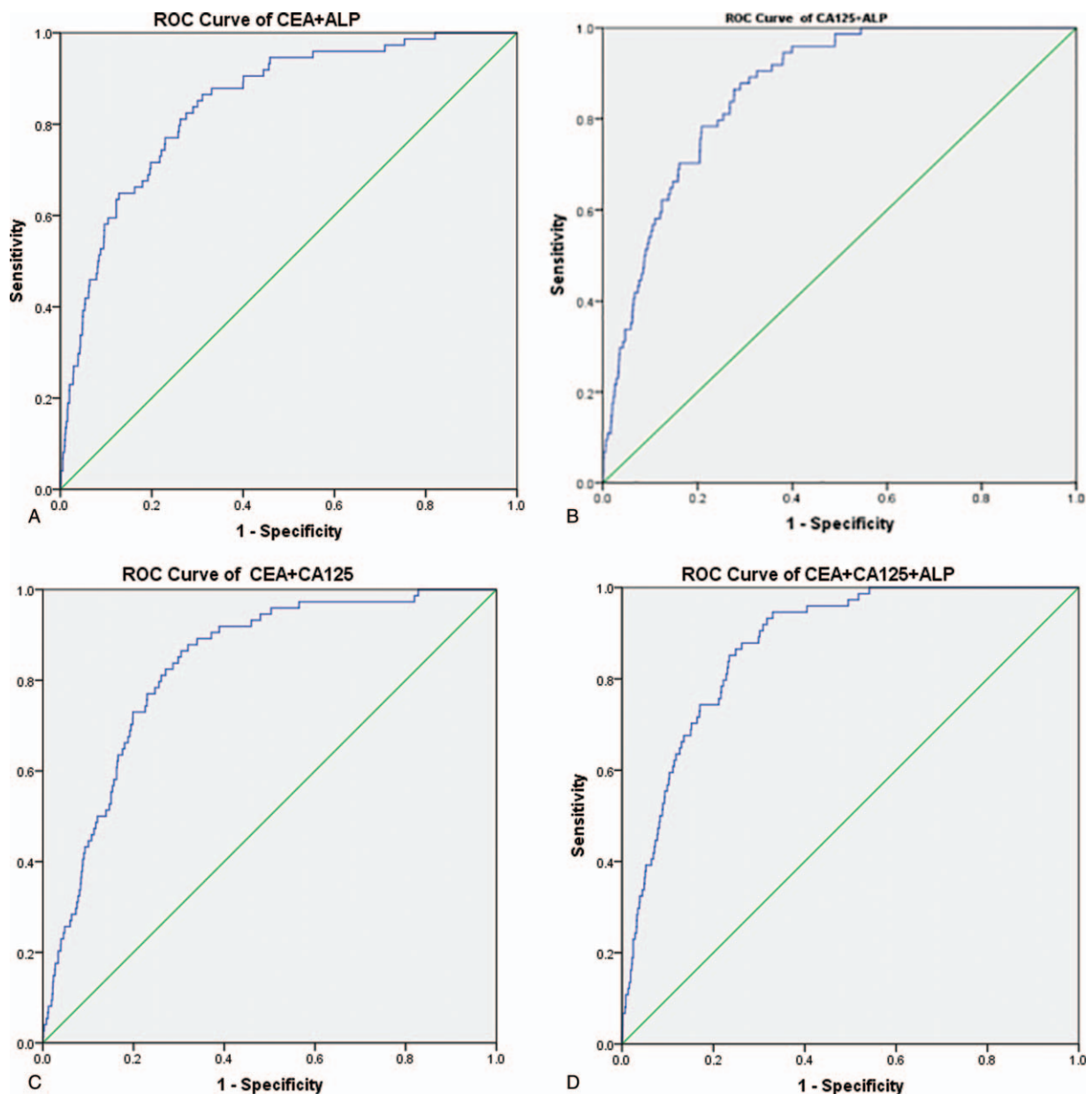

Figure 2. The receiver operating characteristics (ROC) curves of combination of risk factors for diagnosing bone metastases in patients with colorectal cancer. (A) The ROC of CEA+ALP. (B) The ROC of CA125+ALP. (C) The ROC of CEA+CA125. (D) The ROC of CEA+CA125+ALP.

4. Discussion

Bone metastasis is not common in CRC and early diagnosis is relatively difficult.[6] The percentage of BM from patients with primary CRC was between 3.7% and 27%.[12–15] Compared with previous studies, the incidence of BM from CRC in this study was a little low (2.8%). Vatandoust et al[14] reported that signet ring cell cancer of CRC had a high rate of BM (up to 23.7%). But in this study, the rate of signet ring cell carcinoma was low (0.75%). The reason for it may be the number of patients with BM was small in our study. It was well-known that BM often suggested that the cancer had reached a late stage with a poor prognosis.[12] After BM, patients usually suffer a lot of skeletal-related event (SRES), including bone pain, pathological fractures, and spinal cord compression. Thus, in order to dearly diagnose BM and prevent patients' condition from deteriorating, we conducted this study to identify the risk factors for BM from CRC.

In this retrospective study, the spine (62.16%) and pelvis (55.40%) were found to be the 2 most common sites of BM from CRC. And metastasizing to the extremities was rare. These results were in line with Jimi et al's study.[13] A vertebral venous plexus named Baston's plexus was considered to be the main source of BM from CRC.[12,13] Baston's plexus communicates the veins between the peritoneal organs and vertebral bodies. Thus, tumor cells can easy migrate to the vertebrae from peritoneal organs. In addition, the incidence of one site bone metastasis was found to be the highest (67.57%), followed by 2 sites metastases (25.67%). But 3 or more sites BM were rare.

It is reported that tumor biomarkers play an important role in the diagnosis, monitoring, and prognosis of malignant tumors.[16] Based on the analysis, we successfully identified 3 biomarkers as the risk factors for predicting BM from CRC, including CEA, CA125, and ALP. They were helpful for early diagnosing BM and could reduce the radiation from X-ray for patients due to radiographic tests. In previous studies, the tumor location was detected to be an independent risk factor for predicting BM in CRC.[4,17] But this result was not confirmed in our study.

Serum ALP is usually used to evaluate liver function in routine test. It is not only found in liver, but also in kidney and bone. Previous study suggested that elevated preoperative serum ALP could lead to poor survival in patients with CRC.[18] Chen et al[19] revealed that ALP was the independent risk factor for BM in breast cancer. Huang et al[20] indicated that ALP was also the independent risk factor for BM in bladder cancer. Based on the analysis of this study, we finally found that high concentration of ALP was the independent risk factor for diagnosing BM in CRC, with a cut-off value of 85.5 U/L. And it had a relatively high sensitivity and specificity for the diagnosis (81.1% and 71.5, respectively).

As a tumor marker, CEA was widely used in clinical diagnosis, therapy monitoring, and prognosis prediction of breast cancer.[16] It is also applies to patients with CRC. In previous study, Liu et al[21] revealed that a high CEA level in CRC patients with BM was prone to a poor prognosis. And Zhenghong et al[4] suggested that elevated CEA was also one of the risk factors for predicting BM in patients with CRC, which was consistent with our results. As a risk factor for diagnosing BM in CRC, the accuracy of it was good (AUC = 0.791), and the sensitivity and specificity were 81.1% and 70.6%, respectively.

CA125 is a glycoprotein produced by normal epithelial tissue and is often found overexpressed in cancerous tissues. Serum CA125 level was mainly used for the diagnosis, treatment response monitoring, and cancer recurrence of ovarian cancer.[22] Shi et al[23] reported that serum CA125 could help diagnose liver metastases from pancreatic ductal adenocarcinomas and provided a suitable simultaneous resection protocol. CA125 could potentially predict the curability of gastric and cardia cancers, and it was the risk factor of distant metastasis from gastric and cardia cancers.[24] However, to our knowledge, few studies analyzed the relationship between CA125 and bone metastasis in CRC. In this study, the concentration of CA125 > 16.8 mmol/L was identified to be one of risk factors for diagnosing BM from CRC, which indicated that CRC patients with the serum CA125 level >16.8 mmol/L were more likely to develop BM.

Although several risk factors were successfully identified in our study, there were still some limitations in it. First, this was a retrospective study, and the data of patients was just obtained from a single medical institution. Second, some data were lost in our study, such as survival duration and the time to BM. And some data were not reported in the medical reports, including the grade of CRC, intervention, and lymph node metastasis, which would affect the clinical results of this study. Third, the sample size of this study was not large enough. A larger sample patient and multicenter study is helpful to verify the results of our study.

In summary, based on a large population analysis, we successfully identified high serum concentrations of ALP, CEA, and CA125 as the potentially independent risk factors for detecting BM from CRC patients. The specificity of ALP, CEA, and CA125 for detecting BM were 71.5%, 70.6%, and 71.8%, respectively. And the accuracy of ALP, CEA, and CA125 for diagnosing BM were 82.9%, 79.1%, and 80.4%, respectively. MIC1/GDF15 as a bone metastasis biomarker, the specificity of it for diagnosing bone metastasis from prostate cancer, breast cancer, lung cancer, and CRC was 90%, and the accuracy for detecting bone metastasis was 87%.[11] This was higher than our outcome of single factor. But, combined ALP, CEA, and CA125, the specificity and accuracy for diagnosing BM from CRC can also reach to 76.6% and 87.4%, respectively. Combined ALP, CEA, and CA125 have the highest specificity and accuracy for diagnosing BM from CRC. Thus, for a newly diagnosed CRC patient with ALP > 85.5 U/L, CEA > 6.9 mmol/L, and CA125 > 16.8 mmol/L, physicians should pay attention to the BM of them. Because of the limitations in this study, a large sample patients and multicenter study is useful to validate these results.

Author contributions

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References

[1] Fu J-F, Huang Y-Q, Yang J, et al. Clinical characteristics and prognosis of young patients with colorectal cancer in Eastern China. World J Gastroenterol 2013;19:8078–84.
[2] Long Y, Lin M, White L, et al. Global and targeted serum metabolic profiling of colorectal cancer progression. Cancer 2017;123:4066–74.
[3] Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–917.
[4] Zhenghong , Zhu Z, Guoweijian , et al. Retrospective study of predictors of bone metastasis in colorectal cancer patients. J Bone Oncol 2017;9:25–8.

[5] Sun C, Deng Y, Zhou H, et al. Risk factors for the development of metachronous bone metastasis in colorectal cancer patients after curative resection. Int J Surg 2015;21:145–9.

[6] Baek S, Hur H, Min BS, et al. The characteristics of bone metastasis in patients with colorectal cancer: a long-term report from a single institution. World J Surg 2016;40:982–6.

[7] Onesti J, Mascarenhas CR, Chung MH, et al. Isolated metastasis of colon cancer to the scapula: is surgical resection warranted? World J Surg Oncol 2011;9:137.

[8] Bostel T, Förster R, Schlampp I, et al. Spinal bone metastases in colorectal cancer: a retrospective analysis of stability, prognostic factors and survival after palliative radiotherapy. Radiat Oncol 2017;12:115.

[9] Portales F, Mazard T, Ychou M, et al. Bone metastasis in gastrointestinal cancer. Clin Exp Metastasis 2015;32:7–14.

[10] Santini D, Tampellini M, Vincenzi B, et al. Natural history of bone metastasis in colorectal cancer: final results of a large Italian bone metastases study. Ann Oncol 2012;23:2072–7.

[11] Windrichova J, Fuchsova R, Kucera R, et al. MIC1/GDF15 as a bone metastatic disease biomarker. Anticancer Res 2017;37:1501–5.

[12] Cassar N, Cresswell A, Moran B. Oligometastatic colorectal cancer: is single-site bony colorectal metastasis a treatable condition? Int J Colorectal Dis 2017;32:1229–31.

[13] Jimi S, Yasui T, Hotokezaka M, et al. Clinical features and prognostic factors of bone metastases from colorectal cancer. Surg Today 2013;43:751–6.

[14] Vatandoust S, Price T, Karapetis C. Colorectal cancer: metastases to a single organ. World J Gastroenterol 2015;21:11767–76.

[15] Kanthan R, Loewy J, Kanthan S. Skeletal metastases in colorectal carcinomas: a Saskatchewan profile. Dis Colon Rectum 1999;42:1592–7.

[16] Wang W, Xu X, Tian B, et al. The diagnostic value of serum tumor markers CEA, CA19-9, CA125, CA15-3, and TPS in metastatic breast cancer. Clin Chim Acta 2017;470:51–5.

[17] Li A, Käsmann L, Rades D, et al. A scoring system to predict the development of bone metastasis after radical resection of colorectal cancer. Anticancer Res 2017;37:5169–72.

[18] Hung H, Chen JS, Chien-YuhYeh , et al. Preoperative alkaline phosphatase elevation was associated with poor survival in colorectal cancer patients. Int J Colorectal Dis 2017;32:1775–8.

[19] Chen W, Shen JF, Zhou Y, et al. Clinical characteristics and risk factors for developing bone metastases in patients with breast cancer. Sci Rep 2017;7:11325.

[20] Huang P, Lan M, Peng AF, et al. Serum calcium, alkaline phosphotase and hemoglobin as risk factors for bone metastases in bladder cancer. PLoS ONE 2017;12:e0183835.

[21] Liu F, Zhao J, Xie J, et al. Prognostic risk factors in patients with bone metastasis from colorectal cancer. Tumour Biol 2016;[Epub ahead of print].

[22] Babic A, Cramer DW, Kelemen LE, et al. Predictors of pretreatment CA125 at ovarian cancer diagnosis: a pooled analysis in the Ovarian Cancer Association Consortium. Cancer Causes Control 2017;28: 459–68.

[23] Shi H, Jin C, Fu D. Preoperative evaluation of pancreatic ductal adenocarcinoma with synchronous liver metastasis: diagnosis and assessment of unresectability. World J Gastroenterol 2016;22: 10024–37.

[24] Luo T, Luo T, Chen W, et al. CA125 is a potential biomarker to predict surgically incurable gastric and cardia cancer: a retrospective study. Medicine (Baltimore) 2016;95:e5297.