

BMP Signaling Is a Prognostic Marker in Patients With Colorectal Cancer and Associates With Frailty

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Abstract. *Background/Aim:* Bone morphogenetic proteins (BMPs) are members of the transforming growth factor- β superfamily of ligands and have been shown to promote or suppress colorectal cancer (CRC) growth. Developing treatments that target BMPs is challenging due to their multiple roles, including involvement in the inflammatory response and nutritional status. The present study evaluated the prognostic value of BMP-4, which is believed to be highly expressed in CRC, and its correlation with inflammatory and nutrition statuses in patients with CRC. *Materials and Methods:* We analyzed BMP-4 expression in tumor tissues from 144 patients who underwent CRC surgery using immunohistochemistry and evaluated the relationship between BMP-4 levels and clinical outcomes. *Results:* Kaplan–Meier analysis revealed that patients with high expression levels of BMP-4 exhibited a shorter overall survival rate than those with low levels of expression. Multivariate analysis revealed that BMP-4 expression was an independent prognostic factor for overall survival and death from other diseases in CRC patients. Furthermore, high BMP-4 expression was significantly correlated with high C-reactive protein/Albumin ratio, sarcopenia, and

osteopenia. *Conclusion:* BMP-4 is a significant prognostic factor in CRC, particularly in predicting death from other diseases, while also showing associations with inflammatory and nutritional statuses.

The discovery of many biomarkers such as rat sarcoma viral oncogene homolog and B-Raf proto-oncogene, serine/threonine kinase and the development of drug therapies including molecular targeted drugs and immune checkpoint inhibitors for colorectal cancer (CRC) have been reported in recent years (1, 2). Despite these advances, the cancer-related mortality rate of CRC is still higher compared with that of other cancers such as breast cancer and prostate cancer (3). Therefore, many clinical researchers have been searching for other biomarkers or mechanisms that might contribute to drug discovery.

Bone morphogenetic proteins (BMPs) are members of the transforming growth factor- β (TGF- β) superfamily of ligands that bind to type I and type II serine-threonine kinase receptors and transduce signals through Smad and non-Smad pathways (4). Some studies showed that BMPs are highly expressed in CRC and identified a crosstalk between BMP signaling and epidermal growth factor receptor (EGFR) signaling, emphasizing the importance of the inhibition of BMP signaling for CRC growth suppression (5, 6). In contrast, other studies showed that BMPs suppress the growth of CRC (7, 8). Moreover, BMPs have been reported as tumor suppressors and tumor promoters in several cancers (9). Therefore, the roles of BMPs in CRC may be complex.

BMPs are divided into subgroups, including BMP-2/4, BMP-5/6/7/8, BMP-9/10, and the growth differentiation factor-5/6/7, by their structural similarities and ability to bind certain type I receptors (4). BMP-9 has been reported as a prognostic factor in CRC (10). Yokoyama *et al.* reported the correlation between BMP-4 and poor prognosis in an analysis using the GEO database (5). More recently, Zhuo *et al.* reported that BMP-4 has an anti-inflammatory role in inflammatory bowel disease (11), and Sartori *et al.* reported

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that decreased BMPs correlated with skeletal muscle wasting associated with cancer cachexia (12). Thus, BMPs can be a prognostic marker, but the development of treatment that targets BMP is too difficult.

The aim of this study was to investigate the prognostic value of BMP-4 expression in CRC and to evaluate the correlations between BMP-4 and inflammatory and nutritional status. BMP-4 and -7 are highly expressed in CRC (6), so we focused on BMP-4 among many BMP members.

Materials and Methods

Patients. This study included 144 patients who underwent colectomy for CRC at Tottori University Hospital, Yonago, Japan from January 2014 to December 2017 and who were diagnosed with pStage II or III CRC. Classification was performed using the 8th Edition of the Union for International Cancer Control TNM classification. Patients who underwent chemoradiation therapy before surgery, had a history of familial adenomatous polyposis, or had no cancer cells in the specimen because of previous endoscopic surgery were excluded. This study was approved by the institutional review board of Tottori University (No. 23A121).

Immunohistochemical analysis. Immunohistochemistry (IHC) was performed following standard protocols. Briefly, formalin-fixed, paraffin-embedded tissue was processed into 4- μ m-thick sections. After deparaffinizing the tissue blocks, antigen retrieval was performed at 121°C for 10 min in 10 mmol/l sodium citrate (pH 6.0). Endogenous peroxidase in the tissue sections was blocked by incubation with 3% hydrogen peroxide for 30 min, and non-specific protein binding was blocked with 10% Block-Ace (DS Pharma Biomedical, Osaka, Japan) for 30 min. Specimens were incubated with anti-BMP-4 antibody (ab124715, Abcam, Cambridge, UK, dilution of 1:200) at 4°C overnight. The secondary antibody reagent was Histofine Simplestain MAX-P0 (Nichirei, Tokyo, Japan) and color development was performed using a DAB Peroxidase Substrate Kit (Vector Laboratories, Burlingame, CA, USA). Sections were counterstained with hematoxylin.

The expression of BMP-4 in CRC was assessed as the percentage of tumor cells with strongly positive staining, and a two-tiered discrimination using strong or weak staining was used. Tumors with >50% strongly positive cells were classified as high expression tumors, and those with $\leq$ 50% positive cells were classified as low expression tumors. Immunolabeling was evaluated by three investigators (S.S., S.S. and Y.U.); agreement was obtained in each case.

Inflammatory and nutritional markers. We collected the following blood test data from the patients' records: serum Albumin (Alb) level (g/dl), C-reactive protein (CRP) level (mg/dl), and total peripheral blood lymphocyte, platelet, and neutrophil counts (cells/mm³). The CRP/Alb ratio (CAR) was calculated by dividing the serum CRP level by the serum Alb level. The neutrophil/lymphocyte ratio (NLR) was calculated by dividing the peripheral neutrophil count by the peripheral lymphocyte count. The platelet/lymphocyte ratio (PLR) was calculated by dividing the peripheral platelet count by the peripheral lymphocyte count. The prognostic nutritional index (PNI) was calculated as follows: $PNI = 10 \times \text{serum Alb level} + 0.005 \times \text{total peripheral lymphocyte count}$ (13). We determined the bone mineral density (BMD) and

skeletal muscle index (SMI) using preoperative plain Computed Tomography. BMD was measured in the trabecular bone by calculating the average pixel density within a circle of the mid-vertebral core at the bottom of the 11th thoracic vertebra (14). The Skeletal Muscle mass Index (SMI) was calculated by dividing the skeletal muscle area measured at the level of the third lumbar vertebra by the patient's height (cm²/m²) (15). Preoperative osteopenia and sarcopenia were defined as low BMD and low SMI, respectively. The geriatric nutritional risk index (GNRI) was calculated as follows: $1.489 \times \text{serum albumin level (g/l)} + 41.7 \times \text{body weight/ideal body weight (kg)}$ (16). The cachexia index (CXI) was calculated as $SMI \times Alb/NLR$ (17). These data were collected within one month before surgery.

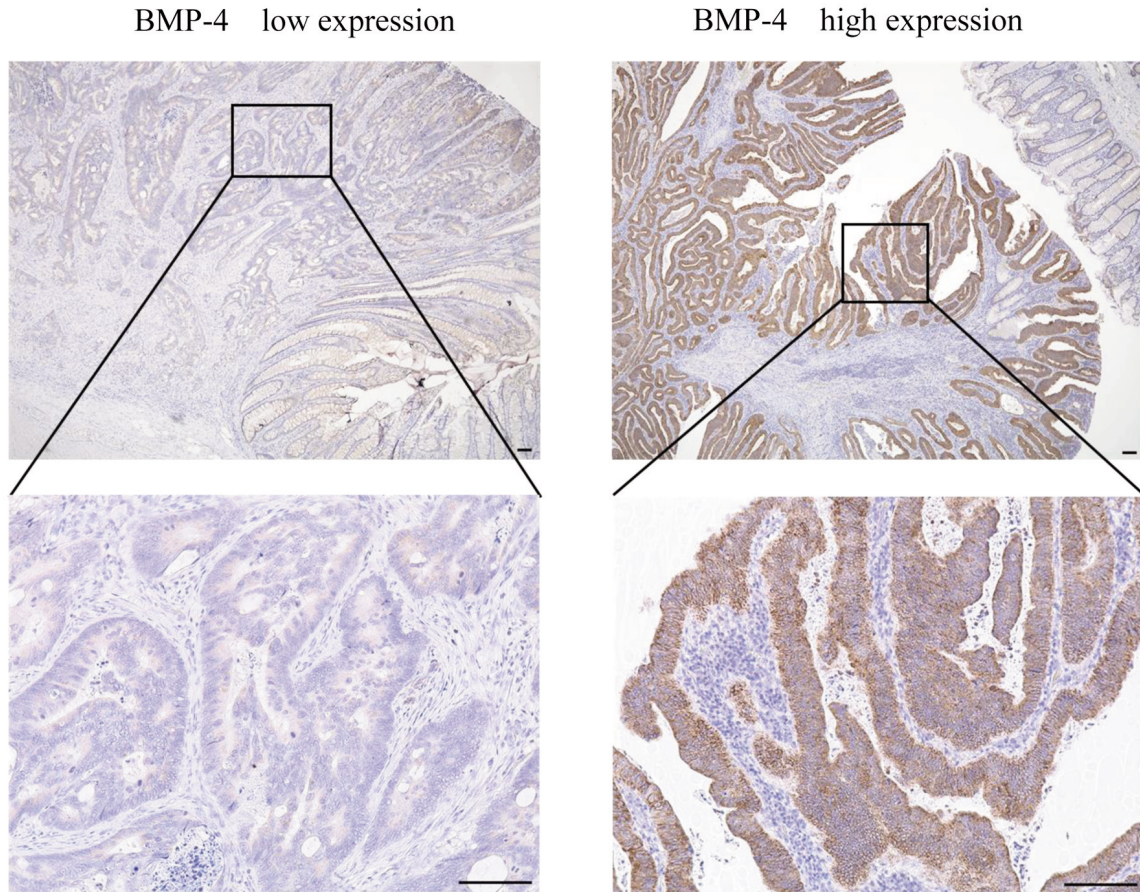
Statistical analysis. Differences in clinicopathological characteristics between two groups were evaluated using the chi-square test for categorical variables and the Mann-Whitney *U*-test for continuous variables. The Youden index was calculated using receiver operating characteristic (ROC) analysis to determine optimal cutoffs for NLR, PNI, PLR, CAR, GNRI, CXI, BMD, and SMI in the survival analysis. Survival curves were calculated using the Kaplan-Meier method. For the analysis of disease-specific survival (DSS), patients who died of causes other than CRC were considered lost to follow-up at the time of death. Differences between the curves were compared using the log-rank test. Cox proportional hazards models were used to evaluate prognostic factors for survival in univariate and multivariate analyses. All statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA). A *p*-value of <0.05 was considered statistically significant.

Results

BMP-4 is a significant prognostic factor in CRC. First, to investigate the expression levels of BMP-4 in CRC, we performed IHC for BMP-4 in 144 CRC tissues from pStage II-III patients. IHC analysis revealed that BMP-4 was overexpressed in tumor cells compared with adjacent normal tissues, and BMP-4 positive staining was predominantly observed in the cytoplasm of cancer cells (Figure 1A). Among the 144 patients, 85 (59%) had high BMP-4 expression. There was no correlation between BMP-4 expression and clinicopathological factors (Table I).

We next investigated whether BMP-4 expression was a prognostic factor for patients with CRC. Kaplan-Meier survival analysis showed that high BMP-4 expression was associated with poor prognosis in patients with pStage II-III. Both overall survival (OS) ($p < 0.001$) and DSS ($p = 0.012$) rates were significantly worse in patients with tumors harboring elevated BMP-4 expression (Figure 1B). While BMP-4 was not an independent prognostic factor for DSS, BMP-4 was an independent prognostic factor for OS (Table II). These results suggested that the percentage of patients who died from other diseases was higher in the BMP-4 high group. More deaths from other malignancies, pneumonia and heart failure were observed in the BMP-4 high group (Table III), and multivariate analysis revealed that BMP-4 was a significant risk factor for death from other diseases (Table IV).

A



B

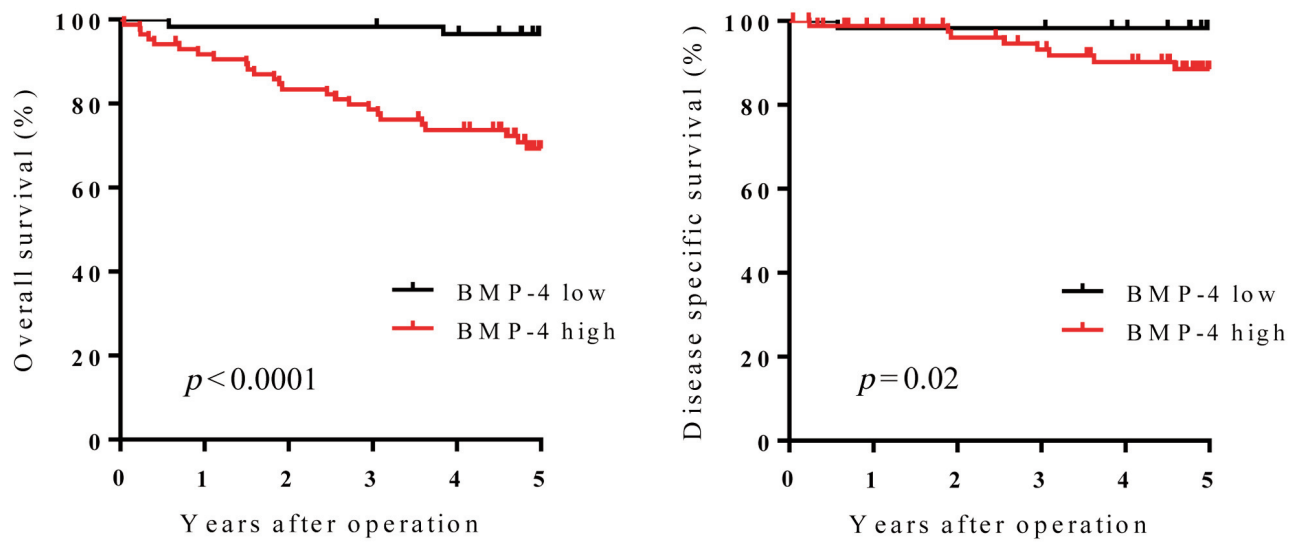


Figure 1. BMP-4 expression in colorectal cancer (CRC) tissue is negatively correlated with prognosis. (A) Representative images of CRC tissue samples immunohistochemically stained for BMP-4. Scale bar: 100 μ m. (B) Correlation between BMP-4 expression and prognosis using the Kaplan-Meier method.

Table I. Clinicopathological factors in CRC patients with low and high BMP-4 expression.

Variables	BMP-4 low (n=59)	BMP-4 high (n=85)	p-Value
Age (years)			
<70	31 (52.5%)	32 (37.7%)	0.076
≥70	28 (47.5%)	53 (62.3%)	
Sex			0.374
Male	31 (52.5%)	51 (60.0%)	
Female	28 (47.5%)	34 (40.0%)	0.409
BMI (kg/m ²)			
<25	43 (72.8%)	67 (78.8%)	0.237
≥25	16 (27.2%)	18 (21.2%)	
Neoadjuvant chemotherapy			<0.001
Yes	2 (3.4%)	7 (8.3%)	
No	57 (96.6%)	78 (91.7%)	0.066
Adjuvant chemotherapy			
Yes	22 (37.3%)	23 (27.1%)	0.193
No	37 (62.7%)	62 (72.9%)	
pStage			0.505
II	30 (50.8%)	48 (56.4%)	
III	29(50.2%)	37 (43.6%)	0.612
Venous invasion			
Negative	6 (11.2%)	11 (13.0%)	0.587
Positive	53 (89.8%)	74 (87.0%)	
Lymphatic invasion			0.063
Negative	6 (10.2%)	11 (13.0%)	
Positive	53 (89.8%)	74 (87.0%)	0.505
pT			
I/II	11 (18.7%)	7 (8.3%)	0.008
III/IV	48 (81.3%)	78 (91.7%)	
pN			0.167
Negative	30 (50.8%)	48 (56.4%)	
Positive	29 (50.2%)	37 (43.6%)	0.055
CEA (ng/ml)			
<5	42 (71.1%)	51 (60.0%)	0.055
≥5	17 (28.9%)	34 (40.0%)	
CA19-9 (U/ml)			
<5	56 (94.9%)	72 (92.9%)	0.055
≥5	3 (5.1%)	13 (7.1%)	

CRC: Colorectal cancer; BMI, body mass index; pT: pathological T classification; pN: pathological N classification; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

Expression of BMP-4 is associated with prognostic inflammatory and nutritional markers. To evaluate survival prediction of several prognostic markers, such as preoperative NLR, PNI, PLR, CAR, GNRI, low SMI (for sarcopenia), low BMD (for osteopenia) and cachexia index, ROC curves were constructed, and the AUC values were compared. These markers reflect the patient's inflammatory or nutritional status, and we reported the effectiveness of these markers to predict prognosis or recurrence in CRC (18, 19). The AUC of CAR was the highest compared with that of other indicators (Table V). High BMP-4 expression was markedly correlated with high CAR, low SMI (sarcopenia) and low BMD (osteopenia) (Table VI).

Discussion

In this study, we evaluated the expression levels of BMP-4 in CRC tissues and demonstrated that elevated expression of BMP-4 was correlated with worse prognosis in patients with stage II/III CRC.

Several studies have examined whether the expression of BMPs or BMP signaling can be a prognostic marker in multiple cancers, including CRC, hepatocellular carcinoma, lung cancer, breast cancer, renal cell carcinoma, ovarian cancer, endometrial cancer, esophageal cancer, and prostate cancer (9). The conflicting roles of BMPs and BMP signaling pathways in cancer have also been reported. For example, in lung cancer, elevated serum BMP-2 levels were observed in many patients (20), but BMP-7-positive tumors were correlated with the absence of bone metastasis (21). In breast cancer, BMP-2/5/6/7 were detected in cancer tissues and the expression of the BMP type IA receptor was correlated with poor relapse-free survival (22); the expression of BMP antagonist was correlated with bone metastasis (23). BMP-7 expression in metastatic prostate cancer tissues was correlated with poor prognosis (24), and reduced BMP-2 expression in cancer tissue was correlated with recurrence (25). The expression of BMPs is detected in many organs, and their roles may vary between cancer sites and non-cancerous regions. Moreover, the influence of BMPs on the tumor environment may vary depending on the type of cancer. Additionally, the types of ligands that bind to BMP receptors, which transduce signals to Smad or non-Smad pathways, vary depending on the types of cancers.

In the present study, we found that BMP-4 expression was correlated with preoperative CAR (determined as the CRP/Alb ratio), sarcopenia and osteopenia in CRC. CRP is an acute-phase reactant regulated by inflammatory cytokines, particularly interleukin (IL)-6 (26). CAR is a serum-based inflammatory indicator linked to poor prognosis in septic patients and several malignancies (27-29). Sarcopenia is likely to be caused by increased protein catabolism, inflammatory reactions, metabolic abnormalities, and poor oral intake in cancer patients. Sarcopenia is associated with cancer cachexia (30). Osteopenia is associated with decreased bone mass and increased bone fragility (31). We previously mentioned that preoperative osteopenia is significant prognostic marker in gastric cancer patients (32). BMP signaling plays a key role in bone formation and homeostasis (33).

Previous studies showed that BMP signaling through Smad promotes muscle growth and protects skeletal muscle from denervation, which induces atrophy (34, 35). Another report showed that BMP-4 enhances the expression of IL-6 and IL-8 (36). Sartori *et al.* showed that IL-6, which is induced by tumor-associated inflammation, induced noggin, a BMP antagonist, and blocked BMP signaling in muscle (12). This may be one possible mechanism for muscle wasting and cancer cachexia.

Table II. Univariate and multivariate analyses of factors associated with disease-specific survival and overall survival.

Variables	Disease-specific survival	Overall survival	
	Univariate analysis Hazard ratio (95%CI) <i>p</i> -Value	Univariate analysis Hazard ratio (95%CI) <i>p</i> -Value	Multivariate analysis Hazard ratio (95%CI) <i>p</i> -Value
Age (≥70)	2.080 (0.537-8.048) 0.289	3.230 (1.309-7.970) 0.011	2.350 (0.932-5.928) 0.07
Sex (male)	1.299 (0.366-4.607) 0.686	2.128 (0.937-4.834) 0.071	
BMI (≥25)	0.300 (0.00-14.868) 0.300	1.003 (0.43-2.339) 0.994	
Depth of invasion (T3/T4)	25.529 (0.012-55837.28) 0.409	4.402 (0.598-32.406) 0.146	
Lymph node metastasis (present)	0.469 (0.121-1.875) 0.838	0.626 (0.289-1.356) 0.234	
Lymphatic invasion (present)	0.469 (0.104-2.359) 0.273	1.701 (0.403-7.175) 0.496	
Venous invasion (present)	1.291 (0.163-10.195) 0.809	1.836 (0.435-7.737) 0.408	
Neoadjuvant chemotherapy (No)	1.553 (0.197-12.271) 0.676	1.926 (0.262-14.177) 0.520	
Adjuvant chemotherapy (No)	1.241 (0.320-4.811) 0.755	2.356 (0.895-6.202) 0.083	
Preoperative CEA (≥5)	2.327 (0.918-5.902) 0.075	2.157 (1.025-4.539) 0.040	1.558 (0.719-3.374) 0.261
Preoperative CA19-9 (≥35)	1.016 (0.129-8.036) 0.988	2.515 (1.018-6.213) 0.046	1.728 (0.677-4.860) 0.253
Postoperative complication (present)	1.972 (0.507-7.665) 0.327	3.228 (1.524-6.839) 0.002	1.026 (1.026-4.860) 0.043
Expression of BMP-4 (high)	7.804 (0.987-61.676) 0.051	10.931 (2.592-46.098) 0.001	8.898 (2.091-37.860) 0.003

BMI: Body mass index; pT: pathological T classification; pN: pathological N classification; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CI: confidence interval.

With respect to osteopenia, Secondini *et al.* reported that Noggin induced by prostate cancer suppressed bone formation and osteoblast recruitment (37). Moreover, osteopenia may be associated with a poor prognosis because cytokines (*e.g.*, parathyroid hormone-related protein, IL-1, and IL-6) derived from tumors activate the NF- κ B pathway in osteoblasts or directly activate osteoclastogenesis (38, 39). Therefore, BMP signaling may be correlated with inflammatory responses and muscle and skeleton frailty. In this study, CRC patients with high expression of BMP-4 were likely to die from other diseases, including pneumonia and heart failure, compared with patients with low expression. Previous studies showed that frailty is associated with susceptibility to or severity of pneumonia and heart failure (40, 41). From these studies, we hypothesize that the inhibition of BMP signaling for tumor growth suppression may contribute to frailty of patients.

Study limitations. First, we did not examine the direct relationship between BMP-4 expression of CRC and prognostic

Table III. Cause of death in colorectal cancer patients with low and high BMP-4 expression.

Variables	BMP-4 low (n=2)	BMP-4 high (n=28)
Primary disease	1 (50.0%)	9 (32.1%)
Other disease	1 (50.0%)	19 (67.9%)
Other cancers		7 (25.0%)
Pneumonia		4 (14.2%)
Heart failure		3 (10.7%)
Urinary tract infection		2 (7.1%)
Aortic aneurysm rupture	1 (50.0%)	1 (3.5%)
Others		2 (7.1%)

inflammatory markers. Second, the cutoff value for defining each marker is not well established; therefore, we used cutoffs from previous reports or ROC analysis. Third, the number of patients in this study was small. Thus, a larger cohort study is

Table IV. Univariate and multivariate analyses of factors associated with death from other diseases.

Variables	Univariate analysis Hazard ratio (95%CI)	p-Value	Multivariate analysis Hazard ratio (95%CI)	p-Value
Age (≥70)	4.377 (1.266-15.126)	0.020	2.959 (0.833-10.513)	0.093
Sex (male)	2.951 (0.971-8.970)	0.056		
BMI (≥25)	1.571 (0.589-4.185)	0.367		
Depth of invasion (T3/T4)	2.725 (0.363-20.484)	0.330		
Lymph node metastasis (present)	0.728 (0.282-1.879)	0.152	2.698 (0.953-7.638)	0.062
Lymphatic invasion (present)	24.348 (0.046-1275.6)	0.318		
Venous invasion (present)	2.38 (0.317-17.89)	0.400		
Neoadjuvant chemotherapy (No)	22.35 (0.006-81390.3)	0.458		
Adjuvant chemotherapy (No)	4.008 (0.921-17.437)	0.064	2.869 (1.123-7.472)	0.028
Preoperative CEA (≥5)	2.327 (0.918-5.902)	0.075		
Preoperative CA19-9 (≥35)	3.164 (1.126-8.891)	0.029		
Postoperative complication (present)	4.143 (1.642-10.452)	0.003		
Expression of BMP-4 (high)	14.049 (1.867-105.69)	0.01	9.950 (1.306-75.777)	0.027

BMI: Body mass index; pT: pathological T classification; pN: pathological N classification; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CI: confidence interval.

necessary. Future studies on the mechanism by which BMPs affect the tumor microenvironment and the entire body are required.

Conclusion

Elevated BMP-4 may be a significant prognostic marker especially for non-CRC-related but frailty-related deaths. Our study indicates BMP-4 is associated with inflammatory and nutritional status in CRC. Future studies are required to elucidate the roles of BMP-4 in other organs in patients with CRC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Study conception and design: S. Sawata, Y. Matsumi and S. Shimizu; Acquisition of data: S. Sawata; Analysis and interpretation of data: S. Sawata and S. Shimizu; Drafting of manuscript: S. Sawata and S. Shimizu; Critical revision: Y. Fujiwara; Final approval of the article: all Authors.

Table V. Comparison of clinical prognostic indicators for overall survival.

Variables	AUC	p-Value
NLR	0.648	0.013
PNI	0.708	<0.001
PLR	0.538	0.524
CAR	0.749	<0.001
GNRI	0.693	0.001
Sarcopenia	0.704	<0.001
Osteopenia	0.729	<0.001
CXI	0.567	0.063

Osteopenia and sarcopenia were defined as low BMD and low SMI, respectively. AUC: Area under the curve; NLR: neutrophil/lymphocyte ratio; PNI: prognostic nutritional index; PLR: platelet/lymphocyte ratio; CAR: C-reactive protein/albumin ratio; GNRI: geriatric nutritional risk index; CXI: cachexia index.

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Table VI. Prognostic indicators in CRC patients with low and high BMP-4 expression.

Variables	BMP-4 low (n=59)	BMP-4 high (n=85)	p-Value
NLR			0.405
High	34 (57.6%)	43 (50.5%)	
Low	25 (42.3%)	42 (49.5%)	
PNI			0.176
High	53 (89.8%)	68 (80.0%)	
Low	6 (10.2%)	17 (20.0%)	
PLR			0.455
High	28 (47.5%)	35 (41.2%)	
Low	31 (52.5%)	50 (58.8%)	
CAR			<0.001
High	10 (17.0%)	45 (52.9%)	
Low	49 (83.0%)	40 (47.1%)	
GNRI			0.098
High	42 (71.1%)	49 (57.6%)	
Low	17 (28.9%)	36 (42.4%)	
Sarcopenia			0.016
Present	22 (37.2%)	49 (57.6%)	
Absent	36 (62.8%)	37 (42.4%)	
Osteopenia			0.039
Present	23 (38.9%)	48 (56.4%)	
Absent	36 (61.1%)	37 (43.6%)	
CXI			0.631
High	24 (40.6%)	38 (44.7%)	
Low	35 (59.4%)	47 (55.3%)	

Osteopenia and sarcopenia were defined as low BMD and low SMI, respectively. CRC: Colorectal cancer; AUC: area under the curve; NLR: neutrophil/lymphocyte ratio; PNI: prognostic nutritional index; PLR: platelet/lymphocyte ratio; CAR: C-reactive protein/albumin ratio; GNRI: geriatric nutritional risk index; CXI: cachexia index.

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