Preoperative Lower Body Mass Index Correlates with Poorer Prognosis in Patients Undergoing Curative Laparoscopic Surgery for Colorectal Cancer

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Abstract. *Aim: The aim of this study was to investigate the correlations between clinicopathological findings, laboratory data and survival outcome in patients undergoing curative laparoscopic surgery for colorectal cancer (CRC). Patients and Methods: Clinicopathological findings and laboratory data, including tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) and systemic inflammatory response indicators, neutrophil-to-lymphocyte ratio (NLR) and modified Glasgow prognosis score (mGPS), for 204 patients (tumor stage I-III) undergoing laparoscopic curative surgery for CRC were collected. Results: Elevated CA19-9 and mGPS, and body mass index (BMI) <20 kg/m^2 were significant indicators of poorer overall survival, while CA19-9 and BMI were validated as independent predictors of overall survival. In addition, BMI <20 kg/m^2 was a significant independent factor predictive of poorer disease-free survival. BMI significantly negatively correlated with NLR, which reflects the patients' immune response. Conclusion: Lower BMI is a promising predictor of recurrence and poor prognosis in patients treated by laparoscopic surgery for CRC with curative intent.*

Colorectal cancer (CRC) is one of the most common types of cancer worldwide (1). Surgical resection is the mainstay of CRC treatment, and laparoscopic surgery for CRC is an acceptable and safe alternative to open surgery, as it has clinical benefit – patients recover earlier from limited invasiveness, fewer postoperative analgesics are required, and the hospital stay is shorter (2, 3). In addition, because the long-term oncological outcome of laparoscopic surgery for CRC is reportedly comparable to that of open surgery (4, 5), laparoscopic surgery is slated to become a more common treatment for patients with CRC.

Routine laboratory data prior to surgery have been demonstrated as predictors of postoperative recurrence and prognosis in patients with CRC. Previous investigators have reported the importance of tumor markers carcinoembryonic antigen (CEA) (6), carbohydrate antigen 19-9 (CA19-9) (7, 8), and systemic inflammatory response (SIR) indicators [neutrophil/lymphocyte ratio (NLR) and modified Glasgow prognosis score (mGPS)] (9-14) as potential indicators for predicting oncological outcomes in CRC. However, the association between these indicators, clinicopathological findings, and oncological outcomes has not been fully evaluated in patients with CRC treated by laparoscopic surgery.

The aim of this study was to investigate the correlations between clinicopathological findings, laboratory data (including tumor markers and SIR indicators), and survival outcome in patients undergoing laparoscopic surgery for CRC with curative intent.

Patients and Methods

Overall, 204 patients who underwent potentially curative laparoscopic surgery for CRC at our institution between January 2004 and December 2013 were enrolled in this retrospective study. Curative resection was defined as the absence of any gross residual tumor in the surgical bed and a surgical resection margin that was pathologically negative for tumor invasion. No patient received chemotherapy or radiotherapy before surgery and no perioperative mortality was observed.

Patients were followed-up, using our standard protocol, every 12-16 weeks for at least 1 year. This protocol included tumor-marker studies, computed tomography, colorectal fiber examinations, ultrasonography, and chest radiography. Bone scans were performed

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when bone metastasis was indicated. The median follow-up time was 30.9 months [95% confidence interval (CI) for the mean was 33.6-41.1 months]. Data collected from inpatient and outpatient records included demographic data [age, sex, height, weight, and body mass index (BMI)], tumor-specific data [tumor location, size, pathologic data including T-classification, lymph node metastasis, differentiation, lymphatic and venous duct invasion, and levels of tumor markers CEA and CA19-9 at diagnosis], operative data (blood loss, operative time, anastomotic leakage, and postoperative complication), and survival data [disease-free survival (DFS) and overall survival (OS)]. Peripheral blood samples were collected from patients prior to surgery, and included the neutrophil and lymphocyte counts for calculating the neutrophil-to-lymphocyte ratio (NLR), albumin level, and C-reactive protein (CRP) level to define the mGPS (13). The mGPS was determined as below. Briefly, patients with elevated CRP levels (>0.5 mg/dl) plus hypoalbuminemia (<3.5 g/dl) were allocated a score of 2 (positive). Patients with only one of these factors were allocated a score of 1 (positive). Patients with neither of these factors were allocated a score of 0 (negative).

The cutoff values for CEA and CA19-9 were 5 ng/ml and 37 U/ml, respectively, according to the normal ranges used at our hospital. The cutoff values for NLR and mGPS were defined as 2.5 and 0. In addition, the cutoff value for BMI was defined as less than the 25th percentile (20 kg/m^2; Figure 1A). Blood collection and subsequent analyses were approved by the Institutional Review Boards of Mie University Hospital in Japan (protocol number: 2216). All participants provided written informed consent and indicated their willingness to donate blood for research.

Statistical analysis. The data are presented as means±standard deviation (SD). Comparisons were made using the Mann–Whitney or Kruskal–Wallis tests, as appropriate. Correlations were analyzed by Spearman's coefficient analysis. Receiver-operating characteristic (ROC) curves were established for determining cutoff values for analyzing prediction of lymph node metastasis and prognosis by Youden's index. Survival curves were obtained using the Kaplan–Meier product limit method, and comparisons were made using the log-rank test. Prognostic factors were examined by univariate and multivariate analysis (Cox proportional hazards regression model). All *p*-values were two-sided and $p<0.05$ was considered statistically significant. All statistical analyses were carried out using Medcalc 7.2 for Windows (Mariakerke, Belgium).

Results

Patients' characteristics. The study group comprised of 101 males and 103 females aged 37-89 years (median=69 years; interquartile range=62-77 years). Staging was principally based on the Union for International Cancer Control /TNM classification of colorectal cancer (15). Overall, 78 patients (39%) had stage I disease, 70 (34%) had stage II, and 56 (27%) had stage III. Starting 4 weeks after curative surgery, pyrimidine fluoride-based regimens were used for 6 months to 1 year in patients classified with stage III disease. Out of the 204 registered patients, 159 (78%) had tumors located in the colon and 45 (22%) had tumors in the rectum. Pathological tumor diameter was the maximum microscopic length of the tumor, irrespective of depth. Histologically-differentiated tumors were noted in 196 patients (96%) and undifferentiated tumors in eight patients (4%). Lymph node metastasis was identified in 56 (27%) patients. In addition, lymphatic invasion was observed in 109 patients (53%) and vascular invasion in 64 patients (31%).

Associations between preoperative tumor markers, SIR markers, BMI, and clinicopathological features. Firstly, we examined the correlation between preoperative tumor markers CEA and CA19-9, SIR markers NLR and mGPS, BMI before surgery, and clinicopathological characteristics. There were significant positive correlations between CEA and CA19-9 (rho=0.301, $p<0.0001$; Figure 1B), CEA and NLR (rho=0.156, $p=0.03$; Figure 1C), and CEA and mGPS (rho=0.197, $p=0.0058$; Figure 1D). In contrast, there were significant negative correlations between BMI and CEA (rho=–0.141, $p=0.0498$; Figure 1E) and BMI and NLR (rho=–0.213, $p=0.0027$; Figure 1F). Table I shows that the preoperative serum CEA level was significantly associated with tumor progression, including high pathological T-stage ($p=0.0002$), lymphatic ($p=0.008$) and vascular ($p=0.0013$) duct invasion, lymph node metastasis ($p=0.0005$), and presence of recurrence ($p=0.017$). In addition, a high mGPS score was significantly associated with high pathological T-stage ($p=0.006$). Furthermore, a low BMI was significantly associated with postoperative recurrence ($p=0.03$).

Identifying independent predictors of poor prognosis in patients undergoing laparoscopic surgery for CRC. OS curves for patients with CRC classified on the basis of CEA, CA19-9, mGPS, NLR, and BMI values prior to laparoscopic surgery are shown in Figure 2. Patients with elevated CEA, CA19-9, and mGPS had significantly poorer OS than patients with levels below the cutoff values (log-rank test: CEA, $p=0.05$; CA19-9, $p=0.0024$; mGPS, $p=0.0166$; Figure 2A-C). In addition, Figure 2E reveals the interesting finding that patients with a BMI <20 kg/m^2 had a significantly inferior prognosis compared to those with BMI >20 kg/m^2. Univariate analysis identified pathological stage T3-4 ($p=0.00049$), poorly-differentiated adenocarcinoma ($p<0.0001$), venous invasion ($p=0.0157$), elevated CA19-9 ($p=0.007$), elevated mGPS ($p=0.0267$), and BMI <20 kg/m^2 as significant prognostic factors for poor OS (Table II). Multivariate analysis using a Cox proportional hazards model showed that pathological stage T3-4 [hazard ratio (HR)=29.8598, 95% confidence interval (CI)=2.0999-424.5951; $p=0.0126$], poorly differentiated adenocarcinoma (HR=24.4823, 95% CI=2.9137-205.7101; $p=0.0034$), elevated CA19-9 (HR=15.5553, 95% CI=2.288-105.7524; $p=0.0052$), and BMI less than 20 (HR=0.0642, 95% CI=0.0126-0.3269, $p=0.001$) were independent predictors of poor prognosis in patients treated with laparoscopic surgery for CRC (Table II).

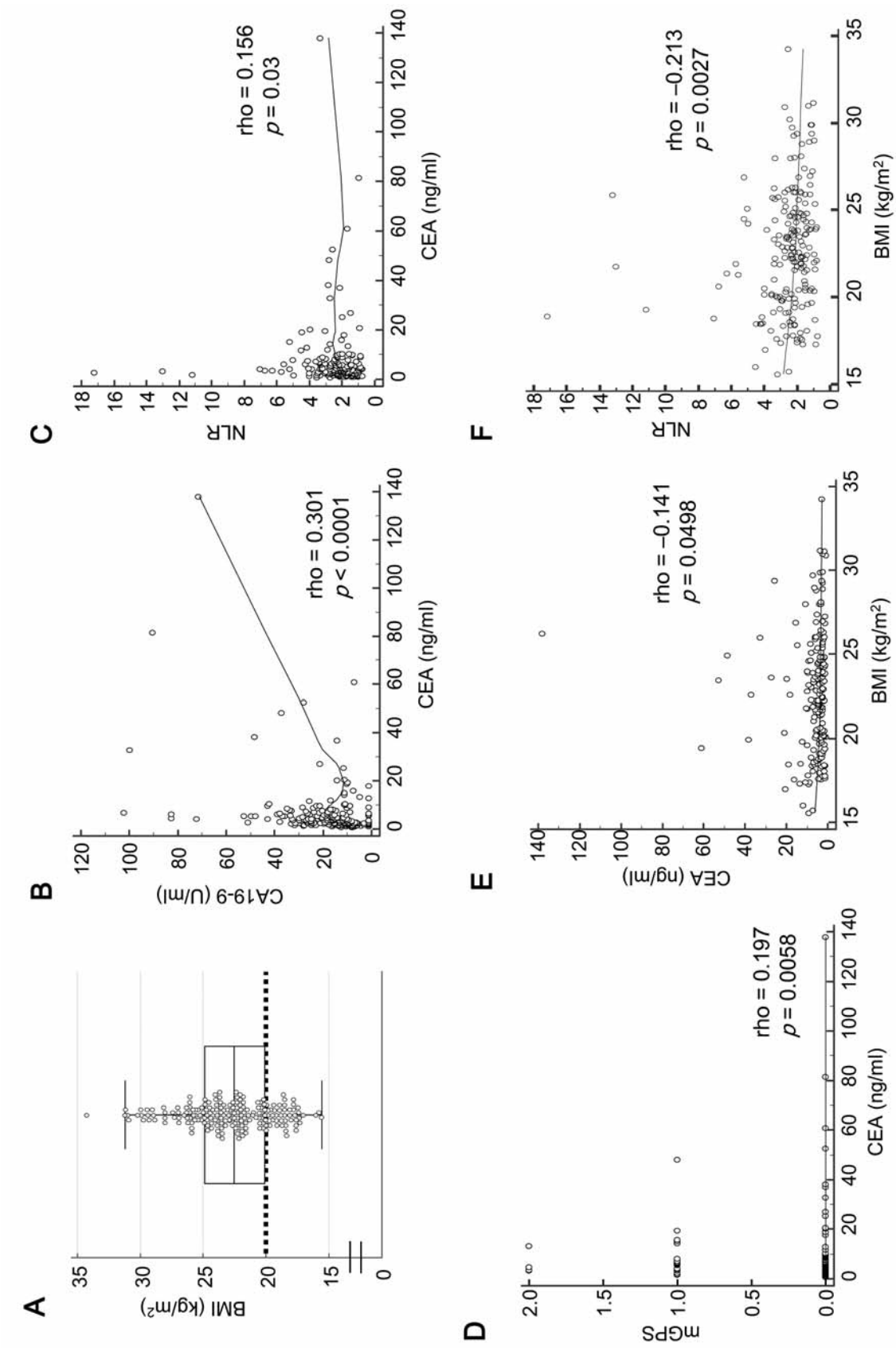

Figure 1. *Distribution of body mass index (BMI) in our cohort and correlation between preoperative tumor markers, systemic inflammatory response (SIR) status, and BMI before laparoscopic surgery for colorectal cancer. A: Distribution of BMI values. The cut-off value for BMI was at the 25th percentile (20 kg/m²). B: Positive correlation between carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9). C: Positive correlation between CEA and neutrophil-to-lymphocyte ratio (NLR). D: Positive correlation between CEA and modified Glasgow prognosis score (mGPS). E: Negative correlation between BMI and CEA. F: Negative correlation between BMI and NLR.*

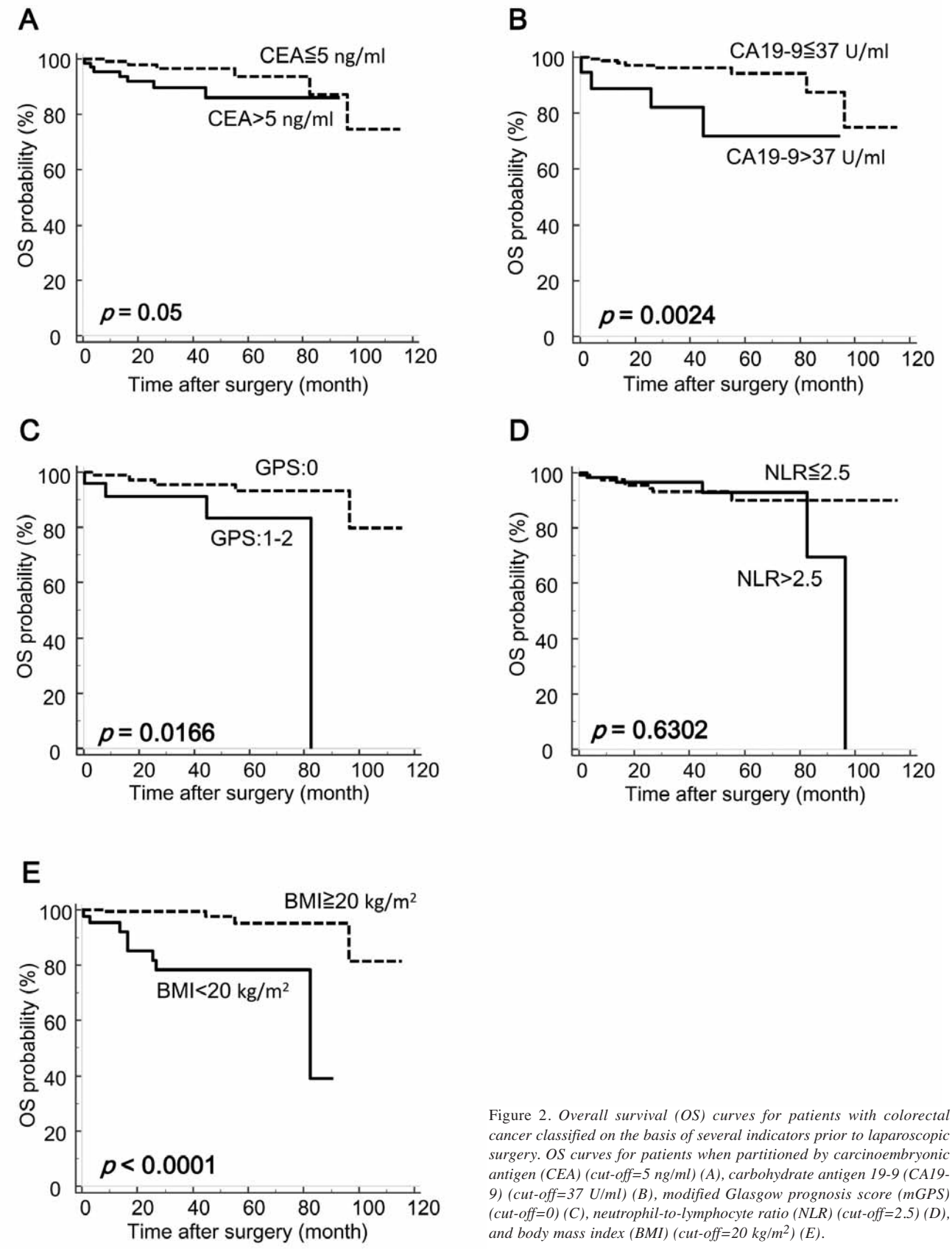

Figure 2. *Overall survival (OS) curves for patients with colorectal cancer classified on the basis of several indicators prior to laparoscopic surgery. OS curves for patients when partitioned by carcinoembryonic antigen (CEA) (cut-off=5 ng/ml) (A), carbohydrate antigen 19-9 (CA19-9) (cut-off=37 U/ml) (B), modified Glasgow prognosis score (mGPS) (cut-off=0) (C), neutrophil-to-lymphocyte ratio (NLR) (cut-off=2.5) (D), and body mass index (BMI) (cut-off=20 kg/m^2) (E).*

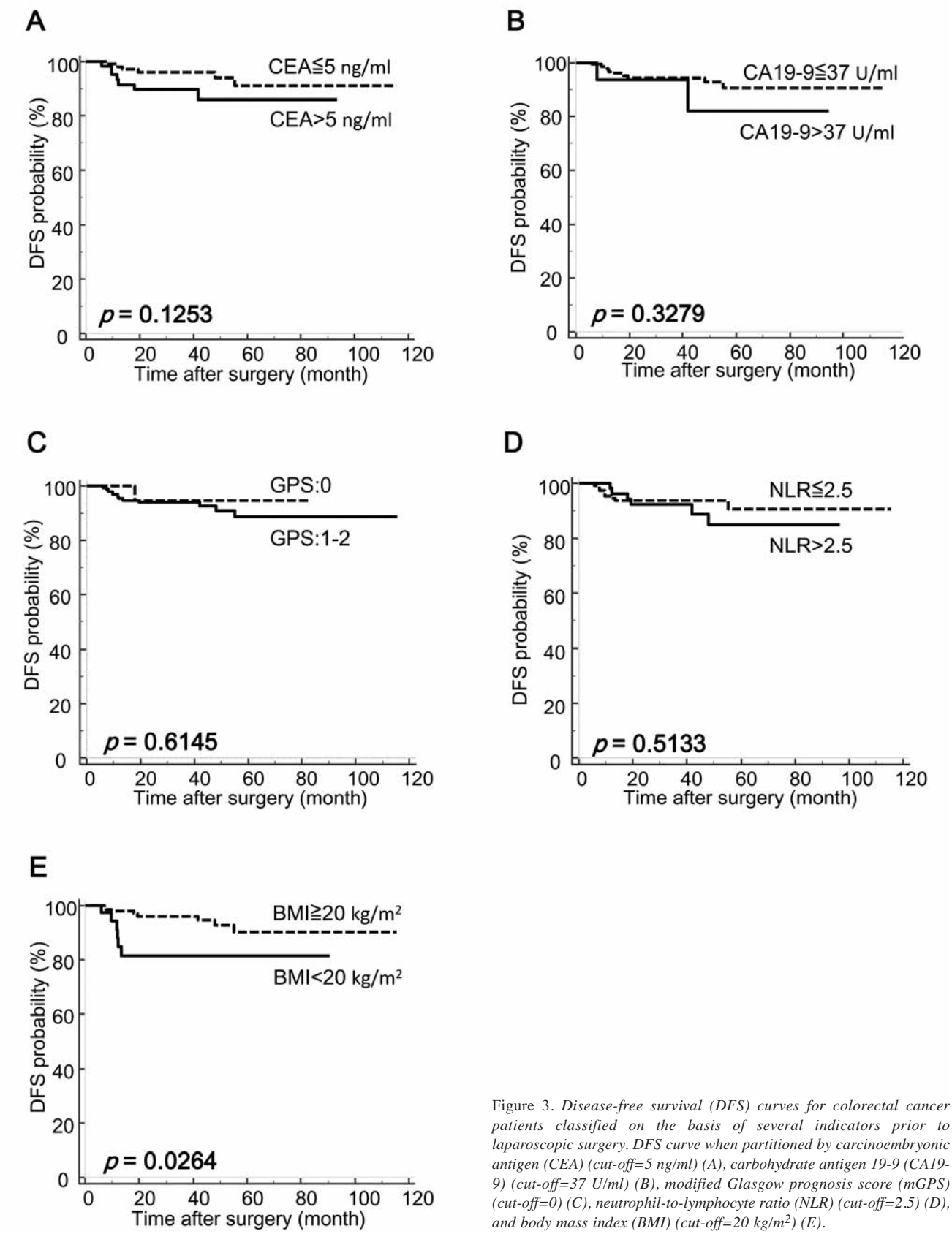

Figure 3. *Disease-free survival (DFS) curves for colorectal cancer patients classified on the basis of several indicators prior to laparoscopic surgery. DFS curve when partitioned by carcinoembryonic antigen (CEA) (cut-off=5 ng/ml) (A), carbohydrate antigen 19-9 (CA19-9) (cut-off=37 U/ml) (B), modified Glasgow prognosis score (mGPS) (cut-off=0) (C), neutrophil-to-lymphocyte ratio (NLR) (cut-off=2.5) (D), and body mass index (BMI) (cut-off=20 kg/m^2) (E).*

Table I. *Association between tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA19-9]), systemic inflammatory response status (neutrophil-to-lymphocyte ratio [NLR] and modified Glasgow prognosis score [mGPS], and body mass index [BMI] and clinicopathological findings.*

Category	CEA (ng/ml)		CA19-9 (U/ml)		NLR		mGPS		BMI (kg/m^2)	
	Mean±SD	*p*-Value	Mean±SD	*p*-Value	Mean±SD	*p*-Value	Mean±SD	*p*-Value	Mean±SD	*p*-Value
Age										
≤69 Years	5.77±7.88	0.004	16.0±13.87	0.001	2.48±2.09	0.285	0.11±0.37	0.229	23.14±3.93	0.287
>69 Years	9.11±17.52		23.19±19.10		2.65±1.84		0.17±0.43		22.42±2.94	
Gender										
Male	6.91±9.04	0.043	17.76±15.85	0.087	2.37±1.45	0.51	0.19±0.49	0.117	23.12±3.64	0.237
Female	7.90±16.96		21.35±17.99		2.75±2.36		0.08±0.28		22.46±3.32	
Pathological T stage										
I-II	4.09±2.81	0.0002	19.57±15.57	0.57	2.53±2.14	0.43	0.07±0.33	0.006	22.83±3.52	0.83
III-IV	10.78±18.50		19.59±18.50		2.59±1.78		0.21±0.45		22.78±3.48	
Pathological N stage										
Negative	5.82±9.43	0.0005	19.85±18.48	0.51	2.62±2.21	0.66	0.11±0.40	0.07	22.78±3.70	0.65
Positive	11.40±20.21		18.83±12.71		2.43±1.14		0.20±0.40		22.82±2.95	
Lymphatic invasion										
Negative	4.82±4.43	0.008	19.59±18.28	0.41	2.38±1.55	0.39	0.10±0.37	0.11	23.28±3.83	0.13
Positive	9.73±17.95		19.61±16.05		2.74±2.27		0.17±0.43		22.42±3.07	
Venous invasion										
Negative	5.52±7.46	0.0013	18.92±16.15	0.55	2.67±2.23	0.39	0.12±0.35	0.58	22.83±3.28	0.68
Positive	11.67±21.27		21.12±19.07		2.34±1.16		0.18±0.50		22.85±3.89	
Pathology										
Mod/well	7.18±12.77	0.60	19.30±16.32	1.0	2.60±2.00	0.20	0.14±0.40	0.98	22.79±3.47	0.89
Poor/muc/sig	13.42±27.66		27.34±31.88		1.84±0.82		0.12±0.35		23.16±4.50	
Recurrence										
No	6.46±9.38	0.017	19.19±16.30	0.90	2.56±2.01	0.80	0.14±0.40	0.60	22.95±3.50	0.03
Yes	20.92±38.40		24.62±26.37		2.59±1.54		0.07±0.27		20.93±2.88	

muc/sig: Mucinous/signet.

Identifying independent predictors of recurrence in CRC patients undergoing laparoscopic surgery. We evaluated which of the factors available in a clinical setting could predict recurrence in patients undergoing laparoscopic surgery for CRC. DFS curves for patients classified according to CEA, CA19-9, mGPS, NLR, and BMI values were generated (Figure 3). Among these factors, BMI <20 kg/m^2 was the only factor associated with significantly poorer DFS (log-rank test; p=0.0264; Figure 3E). Multivariate analysis using a Cox proportional hazards model showed that both poorly-differentiated adenocarcinoma and a BMI <20 kg/m^2 were independent predictive markers for early recurrence in patients treated by laparoscopic surgery for CRC (p=0.0448 and p=0.0254, respectively; Table III).

A BMI of less than 20 kg/m^2 is an indicator of poor prognosis in patients without lymph node metastases from CRC. We also analyzed DFS and OS of patients without lymph node metastases of CRC (stage I-II), who generally do not receive adjuvant chemotherapy after surgery. Our cohort revealed that DFS (log-rank test; p=0.0002; Figure 4A) and OS (log-rank test; p<0.0001; Figure 4B) of patients with BMI <20 kg/m^2 was significantly poorer than patients with BMI ≥20 kg/m^2.

Discussion

In the present study, we demonstrated for the first time that patients with postoperative recurrence had a significantly lower preoperative BMI. In addition, Kaplan–Meier curves for OS and DFS showed that patients with a BMI <20 kg/m^2 had a significantly inferior prognosis compared to those with a greater BMI. Furthermore, multivariate analyses of OS and DFS showed that BMI <20 kg/m^2 was an independent predictor of poor prognosis and early recurrence in patients treated with laparoscopic surgery for CRC with curative intent. Interestingly, BMI was significantly correlated with preoperative NLR, which is a surrogate marker for the immune response to malignancy. A lower BMI prior to surgery may be a promising predictor of early recurrence and poor prognosis in patients treated by laparoscopic surgery for CRC.

Many clinical trials have demonstrated that excess body weight (expressed as a BMI of 25 kg/m^2 or greater) is associated with a risk of adult malignancies, including esophageal, thyroid, gallbladder, endometrial, kidney, and colon cancer (16). In addition, Wu *et al.* showed an association between obesity (BMI ≥30 kg/m^2), but not overweight (BMI=25-29.9 kg/m^2), with increased mortality

Table II. *Univariate and multivariate analyses of overall survival in patients with colorectal cancer treated with curative laparoscopic surgery.*

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (>69 *vs*. ≤69 years)	1.2972	0.4379-3.8423	0.6403	–	–	–
Gender (female *vs*. male)	2.0296	0.6615-6.2269	0.2182	–	–	–
T classification (T3,4 *vs*. T1,2)	9.2936	1.9842-43.5307	0.0049	29.8598	2.0999-424.5951	0.0126
Lymphatic node metastasis (positive *vs*. absent)	2.9128	0.9225-9.1972	0.0698	–	–	–
Pathology (poor/ muc/sig *vs*. mod/well-differentiated)	18.7169	5.4477-64.3067	<0.0001	24.4823	2.9137-205.7101	0.0034
Lymphatic invasion (present *vs*. absent)	2.4757	0.7396-8.2869	0.1434	–	–	–
Venous invasion (present *vs*. absent)	3.9102	1.3005-11.7570	0.0157	0.8311	0.1535-4.4997	0.8309
Blood loss (>30 *vs*. ≤30 ml)	1.0811	0.3051-3.8301	0.9043	–	–	–
Operative time (>218 *vs*. ≤218 min)	0.3265	0.0868-1.2285	0.0995	–	–	–
Anastomotic leakage (yes *vs*. no)	1.5741	0.2075-11.9392	0.9654	–	–	–
Postoperative complication (yes *vs*. no)	1.4882	0.3445-6.4290	0.5479	–	–	–
CEA (>5 *vs*. ≤5 ng/ml)	3.0410	0.9352-9.8887	0.0659	–	–	–
CA19-9 (>37 *vs*. ≤37 U/ml)	5.4405	1.5987-18.5142	0.0070	15.5553	2.288-105.7524	0.0052
mGPS (1-2 *vs*. 0)	4.0533	1.1824-13.8946	0.0267	4.8007	0.9613-23.9753	0.0572
NLR (>2.5 *vs*. ≤2.5)	1.3179	0.4292-4.0464	0.6314	–	–	–
BMI (≥20 *vs*. <20 kg/m^2)	0.0910	0.0242-0.3425	0.0004	0.0642	0.0126-0.3269	0.0010

The median age, blood loss, and operation time were 69 years, 30 ml and 218 min, respectively. Significant associations are shown in bold (p<0.05). HR: Hazard ratio; CI: confidence interval; muc/sig: mucinous/signet; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; NLR: neutrophil-to-lymphocyte ratio; mGPS: modified Glasgow prognosis score; BMI: body mass index.

Table III. *Univariate and multivariate analyses of disease-free survival in colorectal cancer patients treated with curative laparoscopic surgery.*

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (>69 *vs*. ≤69 years)	0.8297	0.2894-2.3786	0.7296	–	–	–
Gender (female *vs*. male)	1.5668	0.5452-4.5028	0.4068	–	–	–
T classification (T3,4 *vs*. T1,2)	4.6296	1.2935-16.5697	0.0191	1.9751	0.3872-10.0755	0.4154
Lymphatic node metastasis (positive *vs*. absent)	3.5375	1.2307-10.1683	0.0196	2.2326	0.6491-7.6792	0.2049
Pathology (poor/ muc/sig *vs*. mod/well differentiated)	7.2063	1.6112-32.2311	0.0101	5.4246	1.0486-28.0622	0.0448
Lymphatic invasion (present *vs*. absent)	5.4485	1.2284-24.1660	0.0265	2.2564	0.3917-12.9964	0.3648
Venous invasion (present *vs*. absent)	4.0122	1.3877-11.6004	0.0107	1.6579	0.4338-6.3357	0.4622
Blood Loss (>30 *vs*. ≤30ml)	0.6653	0.2217-1.9966	0.4696			
Operation Time (>218 *vs*. ≤218min)	0.9979	0.3367-2.9579	0.9970			
Anastomotic leakage (yes *vs*. no)	1.5741	0.2075-11.9392	0.6624			
Postoperative complication (yes *vs*. no)	1.1762	0.3299-4.1932	0.8034			
CEA (>5 *vs*. ≤5 ng/ml)	2.2950	0.7739-6.8058	0.1362	–	–	–
CA19-9 (>37 *vs*. ≤37 U/ml)	2.0992	0.4627-9.5229	0.3389	–	–	–
mGPS (1-2 *vs*. 0)	0.5952	0.0780-4.5391	0.6184	–	–	–
NLR (>2.5 *vs*. ≤2.5)	1.4209	0.4955-4.0748	0.5155	–	–	–
BMI (≥20 *vs*. <20 kg/m^2)	0.3200	0.1114-0.9193	0.0353	0.2810	0.0928-0.8507	0.0254

The median age, blood loss, and operation time were 69 years, 30 ml and 218 minutes, respectively. Significant associations are shown in bold (p<0.05). HR: Hazard ratio; CI: confidence interval; muc/sig: mucinous/signet; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; NLR: neutrophil-to-lymphocyte ratio; mGPS: modified Glasgow prognosis score; BMI: body mass index.

in patients with CRC based on their overall meta-analysis, although considerable heterogeneity was observed across studies (17). These results were consistent in most but not all of the subsequent sub-group analyses, suggesting that a severely rather than mildly-to-moderately high BMI may have an adverse effect on survival in CRC. Similarly to this finding, a recent meta-analysis showed that the survival rate of obese but not overweight adults with leukemia was lower than that for normal-weight patients with leukemia (18). These results support the observation that cancer-related

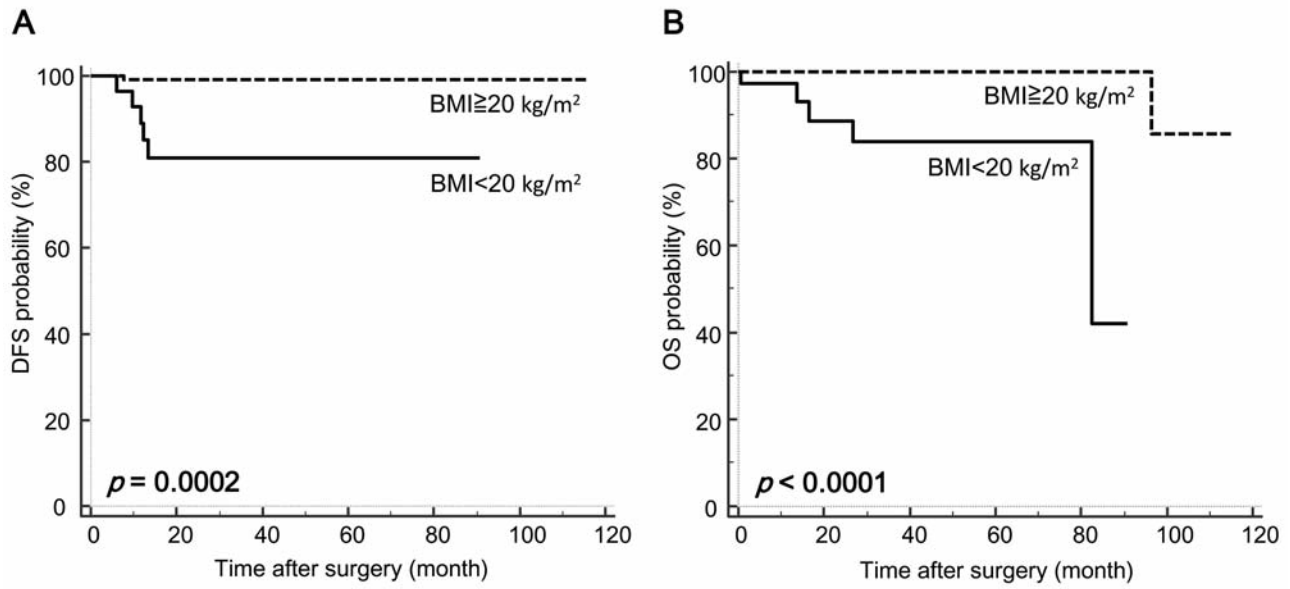

Figure 4. *Survival curves for patients without lymph node metastasis (stage I-II) of colorectal cancer classified on the basis of body mass index (BMI) prior to laparoscopic surgery: A: disease-free survival (DFS), and B: overall survival (OS).*

mortality is increased in obese not overweight people, which was reported by a population-based study (19).

Epidemiologically, the relationship between the risk of mortality and BMI is known to be U-shaped, with increased risk not only being related to cachexia, associated with a very low BMI, but also to obesity, associated with a very high BMI, whereas emerging data indicate that obesity is associated paradoxically with better prognosis in patients with cancer (20). A recent meta-analysis demonstrated that class 1 obese (BMI=25-35 kg/m^2) patients had a 5% lower risk of mortality than those of a healthy weight (21). Moreover, some reports showed that higher BMI protected individuals against poorer outcomes in some malignancies, which is called the 'obesity paradox' (22). In cancer cachexia, which is found in patients with advanced cancer with systemic metastasis, systemic inflammation is induced and persists because of hyper-inflammatory cytokine status. This results in decreased protein anabolism and caloric intake, while promoting an increase in protein catabolism, insulin resistance, lipolysis, and resting energy expenditure. Eventually, loss of muscle mass and strength, loss of whole body fat, ineffective antitumor response and impaired immunity occur, which lead to physical disability, diminished quality of life, and reduced survival (23). In contrast, Sinicrope *et al*. demonstrated from the Adjuvant Colon Cancer Endpoints (ACCENT) database that for patients with CRC (stage II-III) undergoing curative surgery, being underweight (BMI <20 kg/m^2) and not having "cancer cachexia" was significantly associated with increased mortality (24). Our data are consistent with this result as our underweight patients (BMI <20 kg/m^2) treated by curative laparoscopic surgery for stage I-III disease had a phenotype of early recurrence and poor prognosis. Indeed, the patients in our cohort were not afflicted with cancer cachexia because the majority of our cohort had earlier tumor stages (over 70% of patients in this cohort were node metastasis-negative), and there was no correlation between BMI and serum CRP or albumin levels (data not shown).

Although the mechanism involved in the higher risk of recurrence or poor prognosis in patients with underweight status is not fully understood, by analyzing global gene expression changes in patients with renal cell carcinoma, Hakimi *et al*. found that the survival advantage in overweight patients might be related to down-regulation of the fatty acid synthase (*FASN*) gene, and expression levels of the immediately upstream gene for the enzyme acetyl-CoA carboxylase (ACACA), and its encoded protein (22), which are associated with fatty acid metabolism and tumor progression (25). Kuchiba *et al*. also demonstrated that FASN expression levels were lower among obese patients with CRC in the Nurse's Health Study, and suggested that FASN might confer a selective growth advantage to cells upon nutritional depletion (26).

Another potential mechanism we identified in our study was the significant, inverse correlation between BMI and NLR. Recently, elevated preoperative NLR was found to be associated with poor prognosis and tumor recurrence in various malignancies, including CRC (11, 27). One hypothesis

regarding the association between NLR and poor outcome is that relative lymphocytopenia following incremental increase in neutrophils induces a decrease in T4 helper lymphocytes and T8 suppressor lymphocytes, resulting in depletion of innate cellular immunity and increased tumor proliferation and metastasis (28, 29). This evidence suggests that impairment of the anti-tumor immune response might occur in patients who are underweight preoperatively. However, we should further investigate the underlying mechanism of these poorer oncological outcomes to draw definitive conclusions.

In conclusion, although our retrospective study has limitations, including that obese patients as defined in the western world (BMI >30 kg/m^2) accounted for fewer than 5% of our cohort, our findings demonstrate that among patients who are underweight before being treated with laparoscopic surgery for CRC tumor phenotypes might be more aggressive than in patients of normal weight or even those who are obese. Although the underlying mechanisms were not fully investigated, impairment of antitumor immunity might occur in underweight patients and is correlated with higher NLR. Therefore, the preoperative BMI might be a significant predictor of recurrence and prognosis in patients treated by laparoscopic surgery with curative intent for CRC.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in regard to this study.

References

1 Siegel R, Naishadham D and Jemal A: Cancer statistics, 2012. CA Cancer J Clin *62*: 10-29, 2012.

2 Yamamoto S, Inomata M, Katayama H, Mizusawa J, Etoh T, Konishi F, Sugihara K, Watanabe M, Moriya Y, Kitano S and Japan Clinical Oncology Group Colorectal Cancer Study Group: Short-term surgical outcomes from a randomized controlled trial to evaluate laparoscopic and open D3 dissection for stage II/III colon cancer: Japan Clinical Oncology Group Study JCOG 0404. Ann Surg *260*: 23-30, 2014.

3 Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Påhlman L, Cuesta MA, Msika S, Morino M, Lacy AM and Colon cancer Laparoscopic or Open Resection Study Group (COLOR): Laparoscopic surgery *versus* open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol *6*: 477-684, 2005.

4 Leung KL, Kwok SP, Lam SC, Lee JF, Yiu RY, Ng SS, Lai PB and Lau WY: Laparoscopic resection of rectosigmoid carcinoma: prospective randomised trial. Lancet *363*: 1187-1192, 2004.

5 Clinical Outcomes of Surgical Therapy Study Group: A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med *350*: 2050-2059, 2004.

6 Nissan A, Stojadinovic A, Shia J, Hoos A, Guillem JG, Klimstra D, Cohen AM, Minsky BD, Paty PB and Wong WD: Predictors of recurrence in patients with T2 and early T3, N0 adenocarcinoma of the rectum treated by surgery alone. J Clin Oncol *24*: 4078-4084, 2006.

7 Lin PC, Lin JK, Lin CC, Wang HS, Yang SH, Jiang JK, Lan YT, Lin TC, Li AF, Chen WS and Chang SC: Carbohydrate antigen 19-9 is a valuable prognostic factor in colorectal cancer patients with normal levels of carcinoembryonic antigen and may help predict lung metastasis. Int J Colorectal Dis *27*: 1333-1338, 2012.

8 Shibutani M, Maeda K, Nagahara H, Ohtani H, Sakurai K, Toyokawa T, Kubo N, Tanaka H, Muguruma K, Ohira M and Hirakawa K: Significance of CEA and CA19-9 combination as a prognostic indicator and for recurrence monitoring in patients with stage II colorectal cancer. Anticancer Res *34*: 3753-3758, 2014.

9 Walsh SR, Cook EJ, Goulder F, Justin TA and Keeling NJ: Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol *91*: 181-184, 2005.

10 Ding PR, An X, Zhang RX, Fang YJ, Li LR, Chen G, Wu XJ, Lu ZH, Lin JZ, Kong LH, Wan DS and Pan ZZ: Elevated preoperative neutrophil to lymphocyte ratio predicts risk of recurrence following curative resection for stage IIA colon cancer. Int J Colorectal Dis *25*: 1427-1433, 2010.

11 Mallappa S, Sinha A, Gupta S and Chadwick SJ: Preoperative neutrophil to lymphocyte ratio >5 is a prognostic factor for recurrent colorectal cancer. Colorectal Dis 15: 323-328, 2013.

12 McMillan DC: Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care *12*: 223-236, 2009.

13 Toiyama Y, Miki C, Inoue Y, Tanaka K, Mohri Y and Kusunoki M: Evaluation of an inflammation-based prognostic score for the identification of patients requiring postoperative adjuvant chemotherapy for stage II colorectal cancer. Exp Ther Med *2*: 95-101, 2011.

14 Inoue Y, Iwata T, Okugawa Y, Kawamoto A, Hiro J, Toiyama Y, Tanaka K, Uchida K, Mohri Y, Miki C and Kusunoki M: Prognostic significance of a systemic inflammatory response in patients undergoing multimodality therapy for advanced colorectal cancer. Oncology *84*: 100-107, 2013.

15 Hu H1, Krasinskas A and Willis J: Perspectives on current tumor-node-metastasis (TNM) staging of cancers of the colon and rectum. Semin Oncol *38*: 500-510, 2011.

16 Renehan AG, Tyson M, Egger M, Heller RF and Zwahlen M: Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet *371*: 569-578, 2008.

17 Wu S, Liu J, Wang X, Li M, Gan Y and Tang Y: Association of obesity and overweight with overall survival in colorectal cancer patients: a meta-analysis of 29 studies. Cancer Causes Control *25*: 1489-1502, 2014.

18 Castillo JJ, Reagan JL, Ingham RR, Furman M, Dalia S, Merhi B, Nemr S, Zarrabi A and Mitri J: Obesity but not overweight increases the incidence and mortality of leukemia in adults: a meta-analysis of prospective cohort studies. Leuk Res *36*: 868-875, 2012.

19 Faeh D, Braun J, Tarnutzer S and Bopp M: Obesity but not overweight is associated with increased mortality risk. Eur J Epidemiol *26*: 647-655, 2011.

20 Kalantar-Zadeh K, Horwich TB, Oreopoulos A, Kovesdy CP, Younessi H, Anker SD and Morley JE: Risk factor paradox in wasting diseases. Curr Opin Clin Nutr Metab Care *10*: 433-442, 2007.

21 Flegal KM, Kit BK, Orpana H and Graubard BI: Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA *309*: 71-82, 2013.

22 Hakimi AA, Furberg H, Zabor EC, Jacobsen A, Schultz N, Ciriello G, Mikklineni N, Fiegoli B, Kim PH, Voss MH, Shen H, Laird PW, Sander C, Reuter VE, Motzer RJ, Hsieh JJ and Russo P: An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. J Natl Cancer Inst *105*: 1862-1870, 2013.

23 Tan BH and Fearon KC: Cachexia: prevalence and impact in medicine. Curr Opin Clin Nutr Metab Care *11*: 400-407, 2008.

24 Sinicrope FA, Foster NR, Yothers G, Benson A, Seitz JF, Labianca R, Goldberg RM, Degramont A, O'Connell MJ, Sargent DJ and Adjuvant Colon Cancer Endpoints (ACCENT) Group: Body mass index at diagnosis and survival among colon cancer patients enrolled in clinical trials of adjuvant chemotherapy. Cancer *119*: 1528-1536, 2013.

25 Menendez JA and Lupu R: Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. Nat Rev Cancer *7*: 763-777, 2007.

26 Kuchiba A, Morikawa T, Yamauchi M, Imamura Y, Liao X, Chan AT, Meyerhardt JA, Giovannucci E, Fuchs CS and Ogino S: Body mass index and risk of colorectal cancer according to fatty acid synthase expression in the nurses' health study. J Natl Cancer Inst *104*: 415-420, 2012.

27 Halazun KJ, Aldoori A, Malik HZ, Al-Mukhtar A, Prasad KR, Toogood GJ and Lodge JP: Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. Eur J Surg Oncol *34*: 55-60, 2008.

28 Ownby HE, Roi LD, Isenberg RR and Brennan MJ: Peripheral lymphocyte and eosinophil counts as indicators of prognosis in primary breast cancer. Cancer *52*: 126-130, 1983.

29 Hung HY, Chen JS, Yeh CY, Changchien CR, Tang R, Hsieh PS, Tasi WS, You JF, You YT, Fan CW, Wang JY and Chiang JM: Effect of preoperative neutrophil-lymphocyte ratio on the surgical outcomes of stage II colon cancer patients who do not receive adjuvant chemotherapy. Int J Colorectal Dis *26*: 1059-1065, 2011.

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