

Original Article

Overweight (BMI 25-29.9) is Associated with Relatively Favorable Prognosis in Patients with Stage II or III Colon Cancer

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Key Words

Body mass index;

Colon cancer;

Prognosis;

Overall survival;

Disease-free survival

Purpose. This study investigated how body mass index (BMI) affects the prognosis of stage II or III colon cancer.

Methods: In a retrospective review, we examined 1437 patients who underwent surgical treatment for colorectal adenocarcinoma at Taipei Medical University Shuang-Ho Hospital from January 2010 to December 2019. Ultimately, 697 patients with stage II or III colon cancer who underwent curative resection were included in this study. These patients were divided into four groups based on their BMI according to the corresponding World Health Organization definitions. The primary outcomes assessed were overall survival and disease-free survival (DFS).

Results. The patients were categorized as follows: underweight (56 patients, 8.0%), healthy weight (361 patients, 51.8%), overweight (224 patients, 32.1%), and obese (56 patients, 8.0%). In the multivariate analysis of DFS, overweight patients exhibited the most favorable prognoses. Additionally, poor prognostic factors were older age, lymphovascular invasion, perineural invasion, positive surgical margin, and advanced AJCC stage.

Conclusions. Among a sample of patients with stage II or III colon cancer who underwent curative resection, overweight (BMI 25-29.9) demonstrated to be a favorable prognostic factor for DFS.

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Colon adenocarcinoma is a major global health concern, and surgical resection is the standard treatment for stage I to stage III colon adenocarcinoma according to the American Joint Committee on Cancer (AJCC).¹ Regarding the long-term survival of patients with colon cancer, adjuvant chemotherapy also plays a key role in the treatment of stage II or III colon cancer. Therefore, whether patients can undergo a complete course of adjuvant chemotherapy and tolerate chemotherapy toxicity is a critical determinant of prognosis.

Regardless of whether chemotherapy has been administered, several factors influencing the prognosis of colon cancer have been identified.²⁻⁴ However, regarding the effect of body mass index (BMI) on the prognosis of colon cancer, a consensus is yet to be reached. It has been well-established that obesity exerts a detrimental impact on many diseases, including many cancers.⁵⁻⁷ In addition, studies have suggested that being underweight constitutes a risk factor for poor prognosis.^{8,9} Hence, this study investigated which

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of the underweight, normal weight, overweight, and obese groups of a sample of patients categorized on the basis of their BMI exhibited the most favorable prognosis and examined the factors influencing the prognoses of stage II and stage III colon cancers.

Materials and Methods

Patients

We reviewed 1437 consecutive patients who underwent curative resection for colorectal adenocarcinoma from January 2010 to December 2019 at Taipei Medical University Shuang-Ho Hospital. Patients with stage I or stage IV cancer, with carcinoma in situ, with a follow-up period of less than 30 days, with synchronous cancer, or with R2 resection were excluded. The TNM staging system of the AJCC (AJCC/UICC 8th Edition) was used for staging. After exclusion based on the aforementioned criteria, 697 patients were eligible for analysis (Fig. 1). These patients were divided into the aforementioned four BMI groups according to the 2010 World Health Organization definitions: BMI of less than 18.5: underweight; BMI of 18.5-24.9: normal; BMI of 25-29.9: overweight; BMI

of more than 30: obese. From medical charts, we collected patients' demographic and histopathologic characteristics, including age at diagnosis, sex, emergency surgery, surgical method, preoperative carcinoembryonic antigen (CEA) level, tumor size, lymphovascular invasion (LVI), perineural invasion (PNI), tumor grading, tumor location, AJCC stage, number of lymph nodes harvested, adjuvant chemotherapy, surgical margin, and follow-up time (Table 1).

Outcomes

Overall survival (OS) and disease-free survival (DFS) were the primary outcomes. OS was defined as the time from primary tumor resection to death from any cause, and DFS was defined as the time from primary tumor resection to the first cancer recurrence confirmed by radiology or pathology or death from any cause.

Statistical analysis

Continuous variables are presented as medians (Q1-Q3) resulting from the skewed distribution confirmed by Kolmogorov-Smirnov and Shapiro-Wilk tests, and comparisons were made using the Kruskal-

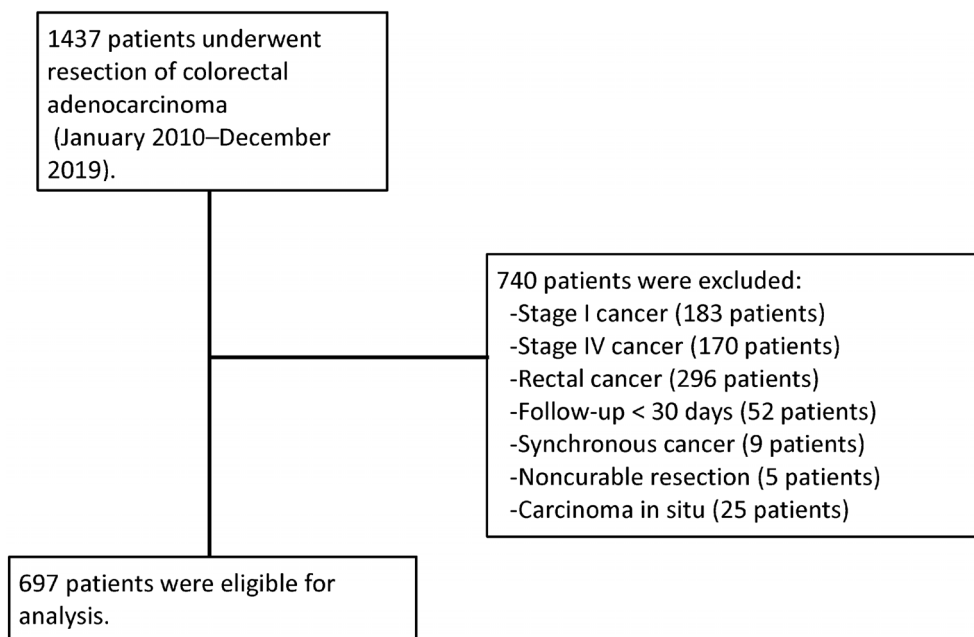


Fig. 1. Flow diagram of colorectal cancer patients analyzed in this study.

Wallis test. Comparisons of categorical variables were made using the chi-squared test. Kaplan-Meier curves were generated to compare OS and DFS according to patients' BMIs. Univariate analysis was performed through Cox regression with hazard ratios (HRs), and 95% confidence intervals (CIs) were estimated to determine the risks of survival outcomes. Variables that might influence DFS (those with $p < 0.2$ in univariate analysis) were all included to subsequent multivariate analysis to minimize the inter-variable interference. A p value of < 0.05 was considered statistically significant.

Results

Clinical and pathological characteristics

After the exclusion of ineligible patients, 697 patients were classified into four groups: underweight (56 patients, 8.0%), normal (361 patients, 51.8%), overweight (224 patients, 32.1%), and obese (56 patients, 8.0%). The patient characteristics are listed in Table 1. We found that patients with lower BMI were more likely to be female and had higher rates of emer-

Table 1. Characteristics of all patients

Characteristic	Underweight (n = 56)	Normal (n = 361)	Overweight (n = 224)	Obese (n = 56)	<i>p</i> value
Age (years)	71 (59.25-81.75)	67.0 (58.0-77.5)	66.0 (58.0-75.8)	64.0 (57.0-68.0)	0.06
Sex, male, n (%)	23 (41.1%)	186 (51.5%)	139 (62.1%)	33 (58.9%)	0.01
Emergency surgery, n (%)					< 0.01
Elective surgery	42 (70.0%)	339 (87.4%)	213 (89.9%)	54 (90.0%)	
Emergency surgery	18 (30.0%)	49 (12.6%)	24 (10.1%)	6 (10.0%)	
Surgical method, n (%)					< 0.01
Open surgery	38 (63.3%)	171 (44.1%)	94 (39.7%)	22 (36.7%)	
Minimally invasive surgery	22 (36.7%)	217 (55.9%)	143 (60.3%)	38 (63.3%)	
Carcinoembryonic antigen	5.9 (2.0-17.3)	4.4 (2.1-12.2)	4.0 (2.2-10.5)	5.2 (2.2-9.4)	0.98
Tumor size (cm)	5.4 (3.9-7.0)	4.6 (3.5-6.1)	4.4 (3.4-5.5)	4.5 (3.2-6.0)	0.03
Lymphovascular invasion, n (%)	35 (58.3%)	226 (58.2%)	126 (53.4%)	31 (51.7%)	0.57
Perineural invasion, n (%)	35 (58.3%)	182 (47.0%)	103 (43.6%)	21 (35.0%)	0.06
Tumor grade, n (%)					0.25
Grade 1-2	55 (91.7%)	359 (93.0%)	227 (96.6%)	56 (93.3%)	
Grade 3-4	5 (8.3%)	27 (7.0%)	8 (3.4%)	4 (6.7%)	
Location ^a					0.046
Left side, n (%)	32 (57.1%)	217 (60.1%)	158 (70.5%)	38 (67.9%)	
Right side, n (%)	24 (42.9%)	144 (39.9%)	66 (29.5%)	18 (32.1%)	
T stage, n (%)					0.89
T1	1 (1.7%)	9 (2.3%)	8 (3.4%)	2 (3.3%)	
T2	1 (1.7%)	23 (5.9%)	11 (4.6%)	5 (8.3%)	
T3	43 (71.7%)	261 (67.3%)	163 (68.8%)	40 (66.7%)	
T4	15 (25.0%)	95 (24.5%)	55 (23.2%)	13 (21.7%)	
N stage, n (%)					0.54
N0	30 (50.0%)	147 (37.9%)	84 (35.4%)	21 (35.0%)	
N1	19 (31.7%)	159 (41.0%)	96 (40.5%)	25 (41.7%)	
N2	11 (18.3%)	82 (21.1%)	57 (24.1%)	14 (23.3%)	
American Joint Committee on cancer stage, n (%)					0.21
II	30 (50.0%)	147 (37.9%)	84 (35.4%)	21 (35.0%)	
III	30 (50.0%)	241 (62.1%)	153 (64.6%)	39 (65.0%)	
Adjuvant chemotherapy, n (%)	31 (51.7%)	253 (65.2%)	161 (67.9%)	46 (76.7%)	0.29
Surgical margin, No. of positive, n (%)	8 (13.3%)	35 (9.0%)	18 (7.7%)	5 (8.3%)	0.58
Follow time (month)	26.37 (11.2-60.1)	35.9 (16.6-62.1)	34.6 (15.2-61.1)	39.6 (18.4-60.7)	0.45

^a Primary tumors located at the cecum, ascending colon, or transverse colon were defined as right sided, whereas primary tumors located at the splenic flexure, descending colon, or sigmoid colon were defined as left sided.

gency surgery and open surgery, larger tumor size, and a higher rate of right-side colon cancer. Owing to the evident differences between underweight and the other groups, we excluded the underweight patients for the purpose of a comprehensive reassessment of patient attributes (Table 2). After the exclusion of underweight patients, the patients with lower BMI were still more likely to be female and to have right-sided colon cancer ($p = 0.04$ and 0.03 , respectively; Table 2).

Survival analyses

Kaplan-Meier curves revealed poorer survival rates

of underweight patients and better survival rates of overweight patients in OS or DFS among the four BMI groups (Figs. 2 and 3, $p = 0.01$ and $p < 0.01$). Further survival analyses of recurrent risks (shorter DFS) were performed using Cox regression (Table 3). In the univariate analysis, the risk factors for shorter DFS were older age (for every 1 additional year in age, HR: 1.02, 95% CI: 1.01-1.03, $p < 0.01$), emergency surgery (HR: 1.74, 95% CI: 1.11-2.71, $p = 0.02$), open surgery (HR: 1.40, 95% CI: 1.02-1.92, $p = 0.04$), high preoperative CEA level (for every 1-ng/mL addition in CEA level, HR: 1.01, 95% CI: 1.00-1.01, $p = 0.01$), LVI (HR: 1.83, 95% CI: 1.31-2.56, $p < 0.01$),

Table 2. Characteristics of patients after exclusion of the underweight group

Characteristic	Normal (n = 361)	Overweight (n = 224)	Obese (n = 56)	p value
Age (years)	67.0 (58.0-77.5)	66.0 (58.0-75.8)	64.0 (57.0-68.0)	0.19
Sex, male, n (%)	186 (51.5%)	139 (62.1%)	33 (58.9%)	0.04
Emergency surgery, n (%)				0.61
Elective surgery	339 (87.4%)	213 (89.9%)	54 (90.0%)	
Emergency surgery	49 (12.6%)	24 (10.1%)	6 (10.0%)	
Surgical method, n (%)				0.54
Open surgery	171 (44.1%)	94 (39.7%)	22 (36.7%)	
Minimally invasive surgery	217 (55.9%)	143 (60.3%)	38 (63.3%)	
Carcinoembryonic antigen	4.4 (2.1-12.2)	4.0 (2.2-10.5)	5.2 (2.2-9.4)	0.92
Tumor size (cm)	4.6 (3.5-6.1)	4.4 (3.4-5.5)	4.5 (3.2-6.0)	0.27
Lymphovascular invasion, n (%)	226 (58.2%)	126 (53.4%)	31 (51.7%)	0.59
Perineural invasion, n (%)	182 (47.0%)	103 (43.6%)	21 (35.0%)	0.13
Tumor grade, n (%)				0.16
Grade 1-2	359 (93.0%)	227 (96.6%)	56 (93.3%)	
Grade 3-4	27 (7.0%)	8 (3.4%)	4 (6.7%)	
Location ^a				0.03
Left side, n (%)	217 (60.1%)	158 (70.5%)	38 (67.9%)	
Right side, n (%)	144 (39.9%)	66 (29.5%)	18 (32.1%)	
T stage, n (%)				0.82
T1	9 (2.3%)	8 (3.4%)	2 (3.3%)	
T2	23 (5.9%)	11 (4.6%)	5 (8.3%)	
T3	261 (67.3%)	163 (68.8%)	40 (66.7%)	
T4	95 (24.5%)	55 (23.2%)	13 (21.7%)	
N stage, n (%)				0.97
N0	147 (37.9%)	84 (35.4%)	21 (35.0%)	
N1	159 (41.0%)	96 (40.5%)	25 (41.7%)	
N2	82 (21.1%)	57 (24.1%)	14 (23.3%)	
American Joint Committee on cancer stage, n (%)				0.89
II	147 (37.9%)	84 (35.4%)	21 (35.0%)	
III	241 (62.1%)	153 (64.6%)	39 (65.0%)	
Adjuvant chemotherapy, n (%)	253 (65.2%)	161 (67.9%)	46 (76.7%)	0.18
Surgical margin, No. of positive, n (%)	35 (9.0%)	18 (7.7%)	5 (8.3%)	0.56
Follow time (month)	35.9 (16.6-62.1)	34.6 (15.2-61.1)	39.6 (18.4-60.7)	0.72

^a Primary tumors located at the cecum, ascending colon, or transverse colon were defined as right sided, whereas primary tumors located at the splenic flexure, descending colon, or sigmoid colon were defined as left sided.

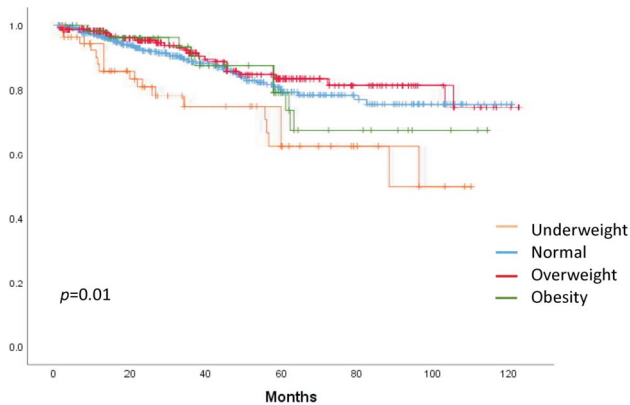


Fig. 2. Kaplan-Meier curves of OS of patients in the four BMI groups.

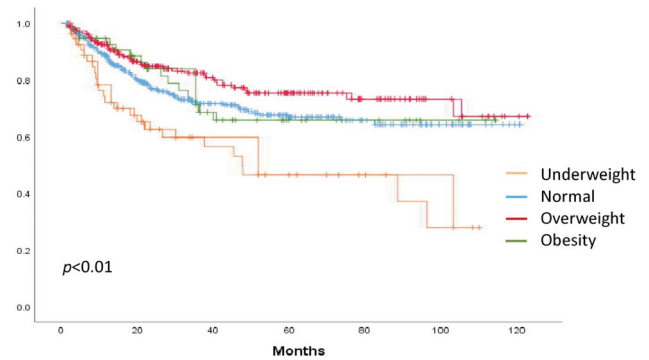


Fig. 3. Kaplan-Meier curves of DFS of patients in the four BMI groups.

Table 3. Univariate and multivariate analyses for DFS in the BMI groups conducted using Cox proportional hazards regression

Characteristic	Univariate analysis (N = 697)		Multivariate analysis ^a (N = 697)	
	HR (95% CI)	p value	HR (95% CI)	p value
BMI		< 0.01		0.03
Normal	1		1	
Underweight	2.02 (1.30-3.14)		1.61 (0.83-3.11)	
Overweight	0.71 (0.49-1.01)		0.68 (0.46-1.01)	
Obese	0.96 (0.55-1.65)		1.36 (0.78-2.38)	
Age (for every 1 additional year in age)	1.02 (1.01-1.03)	< 0.01	1.02 (1.01-1.04)	< 0.01
Sex				
Male	1		1	
Female	1.14 (0.85-1.53)	0.38		
Emergency surgery		0.02		0.76
Elective surgery	1		1	
Emergency surgery	1.74 (1.11-2.71)		1.11 (0.57-2.16)	
Surgical method		0.01		0.02
Minimally invasive surgery	1		1	
Open surgery	1.63 (1.11-2.40)		1.53 (1.08-2.16)	
CEA (for every 1 ng/mL additional in CEA)	1.01 (1.00-1.01)	< 0.01	1.00 (0.998-1.01)	0.32
LVI		< 0.01		0.02
LVI (-)	1		1	
LVI (+)	1.83 (1.34-2.50)		1.57 (1.09-2.26)	
PNI		< 0.01		< 0.01
PNI (-)	1		1	
PNI (+)	2.09 (1.55-2.81)		1.74 (1.24-2.42)	
Surgical margin		< 0.01		< 0.01
R0 resection	1		1	
R1 resection	2.78 (1.87-4.14)		2.06 (1.26-3.36)	
Tumor grade		0.61		
Grade 1-2	1		1	
Grade 3-4	1.17 (0.65-2.10)			
AJCC stage		< 0.01		< 0.01
II	1		1	
III	2.20 (1.57-3.10)	< 0.01	1.75 (1.17-2.62)	
Tumor size (for every additional 1 cm)	1.02 (0.96-1.09)	0.49		
Adjuvant chemotherapy		0.73		
No	1		1	
Yes	1.06 (0.77-1.46)			

^a Only variables with $p < 0.2$ in the univariate analysis were included in the multivariate analysis. BMI, body mass index; LVI, lymphovascular invasion; PNI, perineural invasion.

PNI (HR: 2.08, 95% CI: 1.51-2.87, $p < 0.01$), positive surgical margin (HR: 2.80, 95% CI: 1.84-4.28, $p < 0.01$), and advanced AJCC stage (HR: 2.20, 95% CI: 1.57-3.10, $p < 0.01$). In the multivariate analysis, BMI still influenced DFS significantly ($p = 0.03$); specifically, the overweight patients had a relatively low risk of poor prognosis (HR: 0.68, 95% CI: 0.46-1.01), while underweight showed to be associated with poorer prognosis (HR: 1.61, 95% CI: 3.11). Other risk factors were older age (for every 1 additional year in age, HR: 1.02, 95% CI: 1.01-1.04, $p < 0.01$), open surgery (HR: 1.53, 95% CI: 1.08-2.16, $p = 0.02$), LVI (HR: 1.57, 95% CI: 1.09-2.26, $p = 0.02$), PNI (HR: 1.74, 95% CI: 1.24-2.42, $p < 0.01$), positive surgical margin (HR: 2.06, 95% CI: 1.26-3.36, $p < 0.01$), and advanced AJCC stage (HR: 1.75, 95% CI: 1.17-2.62, $p < 0.01$).

Discussion

This study analyzed more than 600 patients who underwent curative resection for stage II or III colon cancer and had a median follow-up time of nearly 3 years (35.5 months). The multivariate analysis demonstrated that overweight was a favorable prognostic factor for DFS (Table 3). In addition, we discovered poor prognostic factors for DFS in patients with stage II or III colon cancer, including older age, LVI, PNI, positive surgical margin, and advanced AJCC stage; this finding was consistent with those of previous studies.²⁻⁴

High BMI and obesity have been recognized to have negative effects on colorectal cancer and other malignancies.⁵⁻⁷ Other studies have revealed that BMI indicating underweight is a risk factor for poor prognosis in patients with colorectal cancer;^{8,9} this finding is compatible with our study results (Figs. 2 and 3, Table 3). We assumed two theories behind this phenomenon: First, underweight patients may already be experiencing cancer cachexia resulting from significant tumor burden-induced weight loss. These patients were not staged as stage IV at the time of surgery, but they exhibited poorer DFS compared to other patients in the same stage. This difference may suggest the presence of occult metastasis. Second, underweight patients

may be in a state of malnutrition, rendering them relatively incapable of tolerating a full course of adjuvant chemotherapy following curative surgery. Another study assumed that patients who are obese or overweight may experience relatively low chemotherapy toxicity, which results in higher compliance and more favorable outcomes compared with underweight patients.¹⁰ In our study, we also demonstrated that underweight patients tend to be older, have a larger tumor size, and have a lower proportion of those undergoing adjuvant chemotherapy compared with patients in the other groups (Table 1).

After the exclusion of the underweight group, most of the variables were consistent across all the groups, except for sex and tumor side (Table 2). Colon cancer is more prevalent in men,¹¹ and accordingly, men constituted a larger proportion in each group in this study. This male predominance was most pronounced in the overweight group ($p = 0.04$). According to previous studies,^{12,13} the average BMI for men is approximately 24 kg/m², with a difference of 1-3 kg/m² compared with women. Consequently, the significantly higher proportion of men in the overweight group in this study was expected. Additionally, because this study included a higher proportion of men with left-sided colon cancer than those with right-sided colon cancer,¹⁴⁻¹⁶ the overweight group included a significantly higher proportion of left-sided colon cancer cases compared with the other groups.

Our study revealed that the overweight showed to be a favorable prognostic factor for DFS (Table 3). Sinicrope et al. and Aparicio et al. have reported similar findings, namely overweight groups exhibiting higher OS than other groups.¹⁷ Because BMI is calculated solely using height and weight, individuals with the same BMI may have vastly different body compositions. Even individuals with a bodybuilder physique can be categorized as being overweight. Therefore, we posit that being regarded as overweight does not necessarily indicate less healthy status compared with the normal weight group. Previous studies also indicated that the highest survival rates are observed within the overweight range (BMI 25-29.9).¹⁸⁻²⁰ However, for those patients classified as obese group (BMI more than 30), an excess of insulin and IGFs has been found

to inhibit cancer cell apoptosis, leading to a poorer prognosis.²¹⁻²³ Therefore, while overweight is a favorable prognostic factor for DFS, an association with a poorer prognosis is observed when BMI exceeds 30.

In our study, although no statistically significant differences were observed, a relatively high proportion of patients in the higher BMI groups tended to receive adjuvant chemotherapy (Table 2). As mentioned, overweight and even obese patients have been shown to experience lower chemotherapy toxicity, which may contribute to their more favorable overall prognoses.^{10,24} Identifying high-risk populations with poor nutritional status based on BMI or albumin levels prior to chemotherapy initiation or at the time of cancer diagnosis could facilitate the implementation of early nutritional interventions and, consequently, lead to improved overall prognosis.

This study had four primary limitations. First, the population of this retrospective study was recruited from a single institution, which may have contributed to institutional bias. Second, an analysis of underweight patients was not conducted for the following reason: Because we could not distinguish between initially underweight patients and those with underweight caused by cancer cachexia, analysis of underweight patients would have been valueless. Third, no details of mortality causes are provided in this paper. Although we demonstrated the impact of BMI on DFS, we could not identify the incidence of complications associated with obesity (e.g., pneumonia and respiratory failure) or their impact on mortality. Finally, although statistics regarding the proportions of patients receiving adjuvant chemotherapy in the BMI groups were available, data regarding treatment completion or details of chemotherapy toxicity were not available; thus, whether chemotherapy regimens and toxicity or the number of treatment cycles were influenced by BMI in any of the groups remains unclear.

Conclusions

Among a sample of patients with stage II or III colon cancer who underwent curative resection, overweight (BMI 25-29.9) demonstrated to be a favorable

prognostic factor for DFS. For underweight patients showing poorer prognosis, clinicians are recommended to pay close attention to nutritional status and adherence to subsequent adjuvant therapy.

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原 著

在第二期及第三期大腸癌的病人中，體重過重 (BMI 25-29.9) 是較佳的預後因子

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目的 這篇研究旨在探討 BMI 如何影響第二、第三期大腸癌患者的預後

方法 在這篇回顧性研究中，我們檢視了自 2010 年 1 月至 2019 年 12 月間，在台北醫學大學-部立雙和醫院接受大腸直腸癌手術治療的總共 1,437 名患者的病歷。最終，我們納入了接受根治性切除的 697 名大腸癌第二、三期患者進行本研究，這些患者依 BMI 指數並根據世界衛生組織 (WHO) 的定義而分為四組。我們的主要評估指標是整體存活期 (OS) 和無病存活 (DFS)。

結果 病患被分為以下幾個類別：體重過輕 (56 位患者，佔總數的 8.0%)、正常體重 (361 位患者，佔總數的 51.8%)、過重 (224 位患者，佔總數的 32.1%) 和肥胖 (56 位患者，佔總數的 8.0%)。在多變數分析中，我們觀察到體重過重患者呈現更有利的預後。此外我們也發現，不良預後因子包括年齡較大、淋巴血管侵犯 (LVI)、神經周圍侵犯 (PNI)、手術切緣有惡性侵犯以及較高的癌症分期。

結論 在接受根治切除的大腸癌第二、三期患者中，體重過重 (BMI 25-29.9) 是無病存活率 (DFS) 較佳的預後因子。

關鍵詞 身體質量指數 (BMI)、大腸癌、預後、整體存活期、無病存活率。