Original Article
Impact of preoperative and postoperative body mass index on disease-free survival after resection for gastric cancer

Chenxi Li[1,2], Yan Shi[1], Xiaochuan Guo[1,3], Mengjiao Fan[1], Liu Yang[1], Guanghai Dai[1]

[1]Department of Oncology, Chinese People's Liberation Army General Hospital, Beijing, China; [2]Department of Oncology, The First Affiliated Hospital of People's Liberation Army General Hospital, Beijing, China; [3]Department of Lymphoma, Beijing Shijitan Hospital, Beijing, China

Abstract: Objective: To investigate the associations between preoperative and postoperative body mass index (BMI) and disease-free survival (DFS) in patients with gastric cancer. Methods: A total of 434 patients who underwent a curative (R0) resection for gastric cancer between 2011 and 2013 were retrospectively studied. We recorded preoperative BMI, BMI at 1 month after surgery and BMI at 6 months after surgery. All patients were divided into 3 groups according to their BMI: low BMI group (< 18.5 kg/m²), normal BMI group (18.5-25 kg/m²), and high BMI group (≥ 25 kg/m²). Clinical-pathological characteristics, oncologic outcomes, and DFS were collected and compared between the 3 groups. To analyze the effects of changes in BMI from before surgery to 6 months after surgery on DFS, patients were stratified into a stable BMI, increased BMI, and decreased BMI group. DFS was compared between the 3 groups. Results: Regarding preoperative BMI, the 2-year DFS rate was 70.3% in low BMI group, 71.5% in normal BMI group, and 68.8% in high BMI group (P=0.904). No significant differences were observed in DFS according to postoperative BMI. Using changes in BMI to predict DFS, the 2-year DFS rate was 72.2% in the stable BMI group, 91.7% in the increased BMI group, and 64.8% in the decreased BMI group (P=0.149). In a Cox proportional hazards model, a high BMI before surgery, compared to normal BMI, was associated with a lower DFS (hazard ratio 2.64; 95% confidence interval, 1.02-6.84, P=0.045). However, postoperative BMI and BMI change status were also not associated with DFS. Conclusion: Before surgery, normal BMI significantly predicted the higher DFS of patients with gastric cancer compared with the high BMI. However, postoperative BMI and changes in BMI were not independent prognostic factors of DFS.

Keywords: Gastric cancer, body mass index, BMI change status, disease-free survival (DFS)

Introduction

In recent years, despite significant decreases in the incidence and mortality rates of gastric cancer (GC), GC continues to be an important public health problem worldwide [1]. Nearly two-thirds of stomach cancers occur in developing countries, especially in South America and China [1]. In China, GC is the third most frequent cancer diagnosis and cause of cancer-related death [2]. Although the prognosis after gastric resection largely depends on the stage of disease at presentation, other patient-level factors may affect outcomes [3]; body mass index (BMI) may be one of these factors. BMI (calculated as weight [kg]/height [m²]) is often classified as underweight (< 18.50 kg/m²), normal (18.5-24.99 kg/m²), overweight (≥ 25.00 kg/m²), and obese (≥ 30.00 kg/m²) [4]. Several studies have been conducted on BMI and the relationship between BMI and surgical outcomes and survival, such as for colon carcinoma [5], rectum carcinoma [6], endometrial carcinoma [7], carcinoma of the pancreas [8], and hepatocarcinoma [9, 10]. However, the impact of BMI on outcomes after gastrectomy is less well defined. In particular, few studies have focused on the relationship between postoperative BMI, BMI changes and disease-free survival (DFS). The aim of this study was to investi-

Table 1. Patient details (before surgery) and clinicopathological features

	Total (%)	Low BMI Group (%)	Normal BMI Group (%)	High BMI Group (%)	P value
Patient (n)	434	64 (14.7%)	200 (46.1%)	170 (39.2%)	
Preoperative BMI	23.8±4.2	17.6±0.7	22.3±1.5	28.0±2.6	< 0.001
Age (y)	55.2±10.5	55.0±12.7	54.9±10.4	55.8±9.7	0.7080
Sex (male, female)	334:100	42:22	147:53	145:25	0.0018
Tumor site					0.3975
Upper third	124 (28.6%)	18 (14.5%)	56 (45.2%)	50 (40.3%)	
Middle third	121 (27.9%)	17 (14.0%)	57 (47.1%)	47 (38.8%)	
Lower third	155 (35.7%)	20 (12.9%)	70 (45.2%)	65 (41.9%)	
Diffuse	34 (7.8%)	9 (26.5%)	17 (50%)	8 (23.5%)	
pT					0.0511
1	28 (6.5%)	3 (10.7%)	13 (46.4%)	12 (42.9%)	
2	48 (11.1%)	10 (20.8%)	21 (43.8%)	17 (35.4%)	
3	73 (16.8%)	16 (21.9%)	22 (30.1%)	35 (47.9%)	
4	285 (65.7%)	35 (12.3%)	144 (50.5)	106 (37.2%)	
pN					0.5983
0	96 (22.1%)	12 (12.5%)	44 (45.8%)	40 (41.7%)	
1	87 (20.0%)	12 (13.8%)	34 (39.1%)	41 (47.1%)	
2	103 (23.7)	14 (13.6%)	54 (52.4%)	35 (34.0%)	
3a	92 (21.2%)	15 (16.3%)	41 (44.6%)	36 (39.1%)	
3b	56 (12.9%)	11 (19.6%)	27 (48.2%)	18 (32.1%)	
Histological type					0.1475
Adenocarcinoma	256 (59.0%)	37 (14.5%)	118 (46.1%)	101 (39.5%)	
Signet Ring Cell Carcinoma	21 (4.8%)	7 (33.3%)	9 (42.9%)	5 (23.8%)	
Mixed	157 (36.2%)	20 (12.7%)	73 (46.5%)	64 (40.8%)	
Tumor grading					0.6519
Well	14 (3.2%)	2 (14.3%)	7 (50%)	5 (35.7%)	
Moderate	50 (11.5%)	11 (22%)	21 (42%)	18 (36%)	
Poor	370 (85.3%)	51 (13.8%)	172 (46.5)	147 (39.7%)	
Family history of cancer					0.3157
Yes	104 (24.0%)	20 (19.2%)	44 (42.3%)	40 (38.5%)	
No	330 (76.0%)	44 (13.3%)	156 (47.3%)	130 (39.4%)	
Adjuvant chemotherapy					0.9425
Yes	300 (69.1%)	45 (15%)	139 (46.3%)	116 (38.7%)	
No	134 (30.9%)	19 (14.2%)	61 (45.5%)	54 (40.3%)	

gate the relationships of preoperative and postoperative BMI and BMI change status with DFS in patients with gastric cancer.

Materials and methods

In this study, patients who underwent gastrectomy for gastric cancer in our hospital between January 1, 2011 and December 31, 2013 were included. The study was approved by the ethics committee of the Chinese PLA General Hospital, and each subject provided informed written consent. The histological confirmation of neoplasia was preoperatively determined by endoscopic biopsy. Subtotal or total gastrectomy was performed according to tumor location and the possibility of obtaining negative resection margins and a potentially curative (R0) resection. All patients were followed by telephone and clinical data, and the time and metastasis location of tumor recurrence, family history of cancer and time of death were recorded. All patients' follow-up lasted from surgery to May 1, 2016. The endpoint was defined as gastric
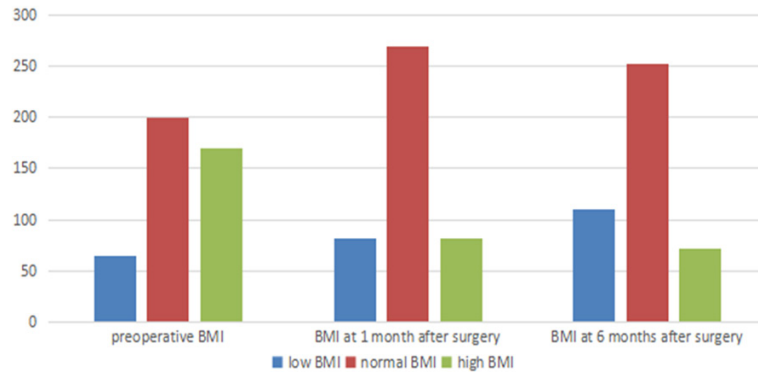
Figure 1. Preoperative and postoperative BMI distribution. Before surgery, most of the patients were in the normal BMI group or the high BMI group, and only a small number of patients in the low BMI group. However, after surgery, the number of patients in the high BMI group decreased significantly, and the number of patients in the normal group and low BMI group increased, especially at 6 months after operation.
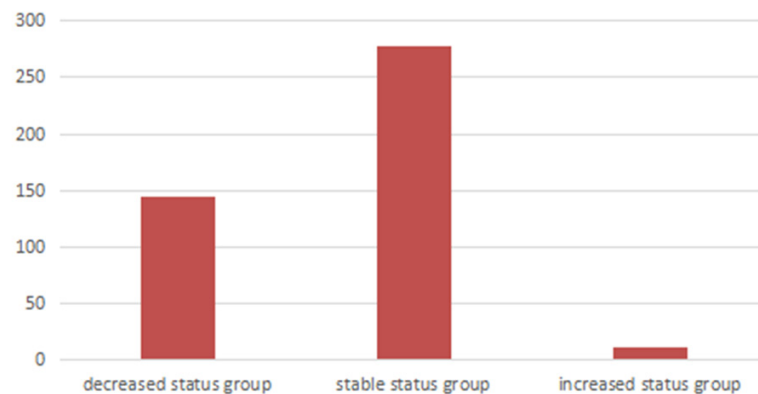

Figure 2. Number of patients in groups by change in BMI status. The changes in BMI from surgery to 6 months after surgery. Weight loss occurred in most patients after surgery, leading to only 12 patients in the increased status group; the other patients were in the stable status group (n=277) and the decreased status group (n=145).

information were excluded from the analysis. All patients were divided into three groups according to BMI level: low BMI group (BMI < 18.5 kg/m²), normal BMI group (BMI 18.5-25 kg/m²), and high BMI group (BMI ≥ 25 kg/m²). The change in BMI from before surgery to 6 months after surgery was recorded, and the change was categorized into 3 groups: stable, increased, and decreased BMI groups.

All analyses were performed with SPSS version 19.0 software. Continuous variables are presented as the mean ± standard deviation (x±s). Variance analysis was used to compare the continuous variables that were not normally distributed. Count data were presented as the percentage (%) and were compared using Pearson's correlation analysis of two variables; additionally, a survival analysis was performed using Kaplan Meier's method, and prognostic factors were investigated in a multivariable analysis using a Cox proportional hazards regression model. A P value < 0.05 (two-tailed) was considered statistically significant.

Results

cancer recurrence or metastasis, and disease-free survival was based on the period from surgery to the end of follow-up or endpoint. The retrospective data included the following: patient age and sex; diagnoses; preoperative body weight and height; body weight and height 1 month and 6 months after surgery; operative site; detailed postoperative pathologic findings; tumor node metastasis (TNM) classification of malignant tumors and cancer stage (the pTNM classification was updated to the 7th edition [11]); and postoperative adjuvant chemotherapy regimen. Patients with metastatic stage IV disease, a non-R0 resection and incomplete

A total of 434 patients who underwent radical operation for gastric cancer in our hospital between January 1, 2011 and December 31, 2013 were included. According to the preoperative BMI categories, there were 64 (14.7%) patients in low BMI group, 200 (46.1%) patients in normal BMI group, and 170 (39.2%) patients in high BMI group. Patient characteristics are summarized in **Table 1**. The mean age was 55.2 y, and the mean BMI was 23.8 kg/m². The majority of patients were male, and the male and female ratio was 334:100. The tumor locations were as follows: upper third in 124 cases (28.6%), middle third in 121 cases (27.9%),
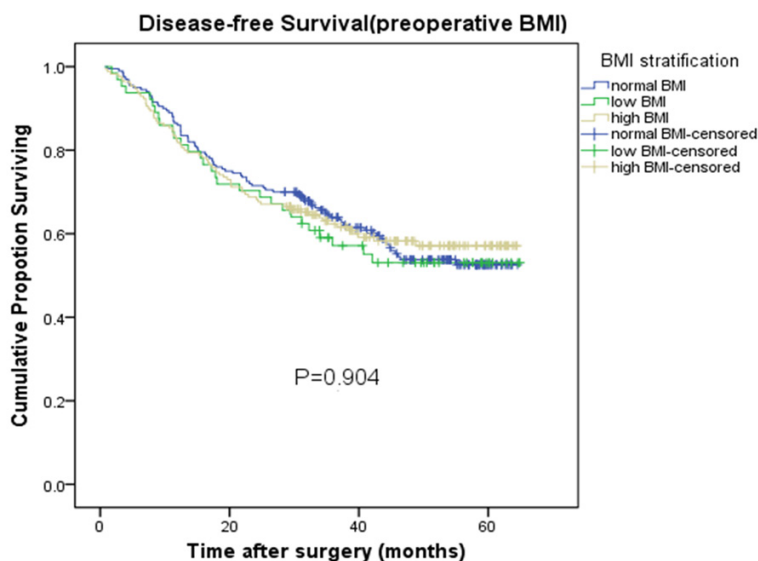
Figure 3. Disease-free Survival in preoperative BMI. Disease-free Survival of patients grouped by BMI before surgery, no significant differences were observed in the low BMI group, normal BMI group and high BMI group (P=0.904).
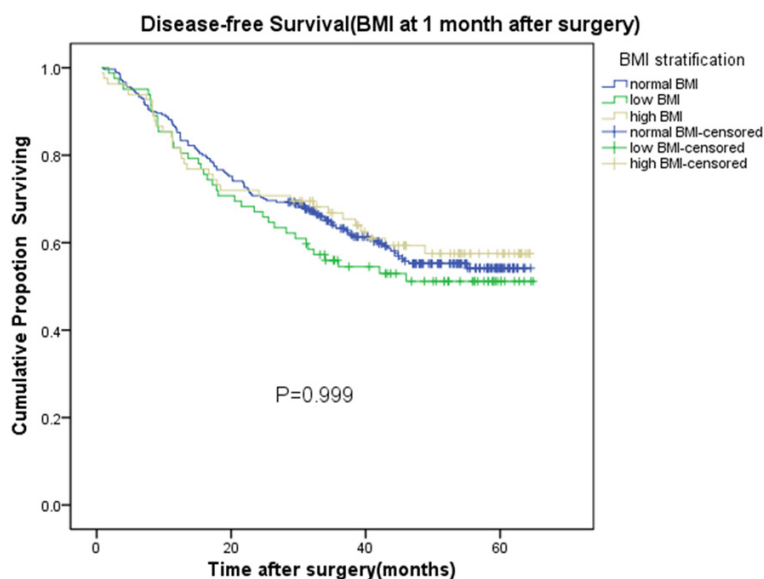

Figure 4. Disease-free Survival in postoperative BMI. Disease-free Survival of patients grouped by BMI at 1 months after surgery, no significant differences were observed in the low BMI group, normal BMI group and high BMI group (P=0.999).

lower third in 155 cases (35.7%), and diffuse in 34 cases (7.8%). Most tumors were locally advanced and penetrated the serosal layer (T4 tumors: n=285, 65.7%). Lymph node metastasis was common (n=338, 77.9%). On pathology, most histological types were adenocarcinoma (n=256, 59.0%) or mixed (n=157, 36.2%), whereas the remaining tumors were signet ring cell carcinoma (n=21, 4.8%). Most pathological grades were poorly differentiated (n=370, 85.3%); only 14 cases (3.2%) were well differentiated, and the others were moderately differentiated (n= 45, 11.6%). Additionally, 104 (24.0%) of the GC cases had a positive family history of malignant neoplasm, whether in first- or second-degree relatives. Of note, there was a higher proportion of males in the normal BMI and high BMI groups, and no significant relationships were found between BMI and tumor site, local depth of invasion, lymph node metastasis, histological type, pathological grading, family history of cancer or adjuvant chemotherapy. **Figure 1** shows the BMI grouping of the patients before and after surgery. Before surgery, 64, 200 and 170 patients were in low BMI group, normal BMI group and high BMI group, respectively. However, 1 month after surgery, the number of patients in the low BMI group and normal BMI group increased to 82 and 270, respectively. In contrast, the number of patients with a high BMI decreased to 82. Finally, 6 months after surgery, the number of patients in the high BMI group was significantly reduced, with only 72 patients in this group, and the number of patients with a low BMI increased to 110. **Figure 2** shows the changes in BMI from surgery to 6 months after surgery. Weight loss occurred in most patients after surgery, leading to only 12 patients in the increased status group; the other patients were in the stable status group (n=277) and the decreased status group (n=145).
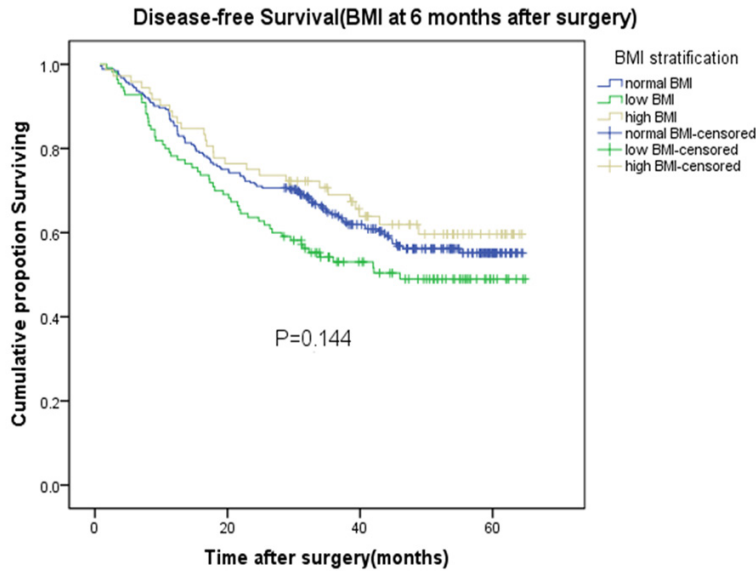
Figure 5. Disease-free Survival in postoperative BMI. Disease-free Survival of patients grouped by BMI at 6 months after surgery, no significant differences were observed in the low BMI group, normal BMI group and high BMI group (P=0.144).
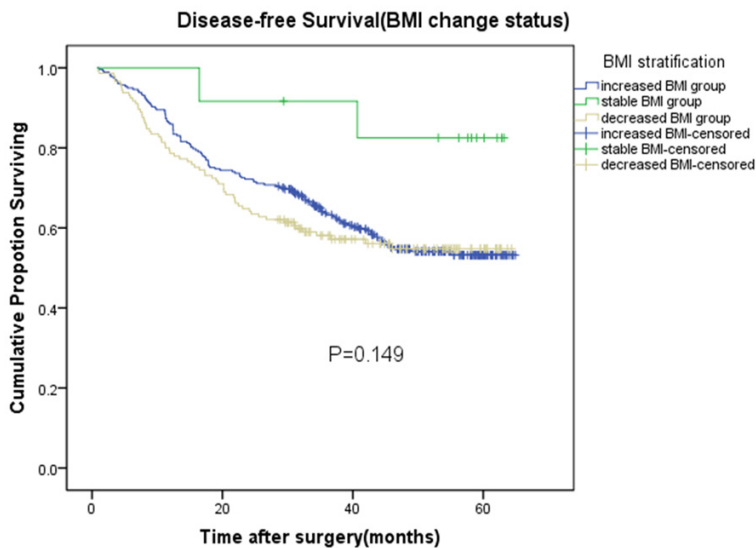

Figure 6. Disease-free Survival in BMI change status. Disease-free Survival of patients grouped by BMI change status, no significant differences were observed in the increased BMI group, stable BMI group and decreased BMI group (P=0.149).

In this study, the mean duration of follow-up was 36.1±18.9 months (range 0.7-64.9 months), which did not differ between the BMI groups. The overall median DFS was not reached. The 1- and 2-year DFS rates were 83.9% and 70.3%, respectively. The DFS curves are shown in **Figure 3** by preoperative BMI group; the 2-year DFS rate was 70.3% in low BMI group versus 71.5% in normal BMI group versus 68.8% in high BMI group (P=0.904). No significant differences were observed in this stratified analysis. **Figures 4** and **5** show the postoperative DFS curves for the three BMI groups. In the Kaplan-Meier curve for BMI 1 month after surgery, although the 2-year DFS rate was greater in the high BMI group than in the low (72.0% versus 67.1%) and normal BMI groups (72.0% versus 70.7%) (**Figure 4**), there were no significant differences in the three groups (P=0.999). In the Kaplan-Meier curve for BMI 6 months after surgery, although the three groups of curves were separated and the 2-year DFS rate differed after the gastric cancer operation (63.6% versus 71.8% versus 75%), on the whole, there was no statistically significant difference in the three groups (P=0.144). Regarding the changes in BMI (**Figure 6**), the analysis showed that the increased status group had a longer 2-year DFS rate compared to the stable status group and the decreased status group (91.7% versus 72.2% versus 64.8%). However, no statistically significant differences were observed in this stratified analysis (P=0.149).

In a Cox proportional hazards model (**Table 2**), postoperative BMI, both 1 month after surgery and 6 months after surgery, and BMI change status were not associated with DFS after adjusting for patient age, sex, tumor site, tumor stage, histological type, pathological grading, family history of cancer, and adjuvant chemotherapy.

Table 2. Multivariate analysis showing independent effects on disease-free survival

	B value	Hazard ratio	95% CI	P value
Preoperative BMI				0.097
Low BMI	-1.19	0.33	0.11-1.02	0.053
Normal BMI	--	1		
High BMI	0.971	2.64	1.02-6.84	0.045
BMI at 1 month after surgery				0.54
Low BMI	0.349	1.42	0.76-2.63	0.27
Normal BMI	--	1		
High BMI	-0.029	0.97	0.57-1.64	0.914
BMI at 6 months after surgery				0.18
Low BMI	0.852	2.34	0.92-6.00	0.074
Normal BMI	--	1		
High BMI	-0.937	0.39	0.13-1.81	0.096
BMI change status				0.31
Stable BMI group	--	1		
Increased BMI group	0.099	1.1	0.19-6.30	0.912
Decreased BMI group	-0.754	0.47	0.16-1.36	0.164
Age (years)				0.41
< 60	--	1		
≥ 60	-0.137	0.87	0.63-1.21	0.41
Sex (male, female)				0.87
Male	--	1		
Female	0.032	1.03	0.71-1.51	0.87
Tumor site				0.005
Upper third	--	1		
Middle third	0.532	1.7	1.12-2.59	0.013
Lower third	0.344	1.41	0.94-2.13	0.101
Diffuse	0.958	2.61	1.50-4.54	0.001
pT				0
1	--	1		
2	-0.250	0.78	0.17-3.57	0.748
3	1.696	5.45	1.60-18.56	0.007
4	2.183	8.87	2.74-28.77	0
pN				0
0	--	1		
1	1.906	6.73	3.18-14.23	0
2	2.258	9.57	4.48-20.42	0
3a	2.604	13.52	6.36-28.72	0
3b	3.351	28.53	13.27-61.33	0
Histological type				0.116
Adenocarcinoma	--	1		
Signet Ring Cell carcinoma	0.740	2.10	1.04-4.22	0.039
Mixed	0.085	1.09	0.79-1.50	0.597
Tumor grading				0.03
Well differentiated	--	1		
Moderate differentiated	0.623	1.86	1.17-2.97	0.009
Poorly differentiated	-0.020	0.98	0.33-2.89	0.971
Family history of cancer				0.906
Yes	--	1		
No	0.022	1.02	0.71-1.47	0.906
Adjuvant chemotherapy				0
Yes	-1.076	0.34	0.25-0.47	0
No	--	1		

However, regarding the preoperative BMI, compared with patients with a normal BMI, the disease-free survival was lower in the high BMI group (adjusted hazards ratio =2.64; 95% confidence interval =1.02-6.84). In addition, increasing T-stage and lymph node stage, middle third or diffuse tumor, signet ring cell carcinoma, not well differentiated, and not completed standardized adjuvant chemotherapy all indicated a lower DFS rate.

Discussion

With the improvements in people's living conditions, there is an increasing number of people who are overweight or obese. It is well known that obesity is associated with cancer incidence and mortality, hypertension, and heart disease [12]. BMI is the standard indicator for evaluating the quality of the body, which is closely related to the occurrence and development of gastric cancer [13]. However, the role of BMI in the prognosis of gastric cancer is not as well understood. Therefore, this study examined the impact of preoperative and postoperative BMI and BMI change status on disease-free survival after resection for gastric cancer.

We retrospectively analyzed 434 cases who underwent radical operation for gastric cancer and were followed for 36.1±18.9 months (range 0.7-64.9 months). Our study demonstrated a negative association between preoperative BMI, postoperative BMI and DFS

in the univariate analysis. In the multivariate analysis, however, before surgery, although the low BMI was not found to be impact DFS, the normal BMI group had a higher DFS rate compared to the high BMI group after adjusting for patient age, sex, tumor site, tumor stage, histological type, pathological grading, family history of cancer, and use of adjuvant chemotherapy. According to the postoperative BMI groups (whether BMI 1 month after surgery or BMI 6 months after surgery), the low BMI group seemed to have a lower DFS rate. Similarly, according to the change in BMI groups, patients with an increase in BMI seemed to not be prone to recurrence after surgery. However, after statistical analysis, postoperative BMI and BMI change status were also not associated with DFS in a Cox proportional hazards model.

Preoperative BMI and DFS

In recent years, people have investigated the relationship between obesity and the prognosis of cancer. In breast cancer, obesity, whether at cancer diagnosis or after diagnosis, is related to poor outcomes [14]. In prostate cancer, obese patients have lower rates of DFS after radical operation and higher rates of death from prostate cancer [15]. In colon cancer, obese patients showed a trend toward worse DFS and OS, whereas overweight patients had a better OS [16]. Regarding gastric cancer, several studies have focused on the effects of obesity on cancer survival, but the results are inconclusive [3, 17, 18]. Dhar et al. reported that patients with a high BMI were at an increased risk of inadequate nodal sampling during gastric cancer resection, which in turn could lead to a higher risk of local recurrence [19]. In contrast, some studies suggest that a high BMI is not a risk factor for either DFS or OS in patients undergoing gastric resection for adenocarcinoma [3, 17, 20]. Additionally, some studies have proposed the "obesity paradox" theory and have suggested that GC patients with a high BMI who receive gastrectomy exhibit a paradoxically "superior" survival outcome compared with normal BMI patients [21, 22]. The mechanisms underlying the effects of BMI on the prognosis of gastric cancer remain poorly understood, but they may involve the inflammatory response, immune system, adipokines and others. Therefore, we need intensive studies on this topic. However, there are few inten-

sive studies on the relationship between low BMI and gastric cancer prognosis. Most studies have noted that low BMI did not impact DFS. This is consistent with our study.

Postoperative BMI, BMI change and DFS

Previous studies have analyzed the relationship between preoperative BMI and DFS. However, unlike other surgeries, gastrectomy is always accompanied by a decrease in body weight. Therefore, postoperative BMI and BMI change are worth noting. Prominent losses in body weight and abdominal fat are observed in the first 3 months after gastrectomy in patients with early gastric cancer, after which the patient's weight tends to stabilize [17]. Accordingly, we analyzed the effects of BMI 1 month and 6 months after the operation as well as of changes in BMI (difference between preoperative BMI and BMI 6 months after surgery) on DFS. One recent study reported that compared with preoperative BMI, BMI 1 year after surgery significantly predicted the long-term survival of patients with gastric cancer but was not independently associated with either disease-specific survival or recurrence-free survival, which is consisted with our findings [17]. Most gastric cancer patients suffer from malnutrition because of esophagitis or because of dumping syndrome and cachexia from the cancer itself and the impact of the gastrectomy. Researchers believe that nutritional improvements can lead to weight gain in patients with gastric cancer undergoing gastrectomy and may lengthen survival [17]. In addition, hormonal changes after gastrectomy should be noted. Patients undergoing gastrectomy commonly have impaired ghrelin production, which secretes growth hormones, increases food intake, and causes weight gain [23, 24]. In our study, although we did not find a significant relationship between postoperative BMI, change in BMI and DFS, the trends are shown in **Figures 5** and **6**; specifically, the high BMI group and increased BMI group showed better disease-free survival after surgery. Therefore, post-gastrectomy patients should be supported with nutritional supplementation.

This study has several limitations. First, this is a retrospective, single-center study, and thus the patients are less representative than those in a multi-center study. Second, due to the short

follow-up time, the overall median DFS was not reached, and thus we cannot discuss the relationship between BMI and OS.

In conclusion, BMI, both after surgery and BMI change, was not a prognostic factor for DFS in patients with gastric cancer undergoing radical operation. However, before surgery, normal BMI significantly predicted the higher DFS of patients with gastric cancer compared with the high BMI. In addition, for low BMI patients, adequate nutritional support should be considered after surgery.

Disclosure of conflict of interest

None.

Address correspondence to: Guanghai Dai, Department of Oncology, Chinese People's Liberation Army General Hospital, Beijing, China. E-mail: daigh60@sohu.com

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