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Original article

A paradox between preoperative overweight/obesity and change in weight during postoperative chemotherapy and its relationship to survival in stage II and III colorectal cancer patients

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SUMMARY

Background & aims: The roles of obesity and weight management in colorectal cancer (CRC) recurrence and survival have gained a considerable amount of attention. However, whether a change in weight affects the risk of recurrence and death remains unclear.

Methods: A retrospective study was conducted using Kaplan–Meier curves, multivariable Cox proportional hazards models, and restricted cubic splines in 902 patients with stage II and III CRC to investigate the impact of the preoperative BMI and change in weight during postoperative chemotherapy on disease-free survival (DFS) and overall survival (OS).

Results: The lowest risk of cancer events (recurrence/metastasis and new CRC cases) and death occurred in patients who had a normal weight (BMI range from 18.5 to 23.9 kg/m^2) or had weight gain of < 5%; the patients who were underweight (BMI $\leq$ 18.5 kg/m^2) or overweight/obese (BMI $\geq$ 24.0 kg/m^2) and had weight loss or weight gain of $\geq$ 5% had a higher risk of cancer events and death. The association between preoperative BMI and the risk of cancer events and death exhibited U-shaped curves; the inflection points were at BMI = 24 kg/m^2 and BMI = 25 kg/m^2 for the risk of cancer events and death, respectively. The association between the change in weight and risk of death also exhibited a U-shaped curve, while the association between the change in weight and risk of cancer events was nearly linear. Multivariable Cox proportional hazards models showed that the preoperative BMI and change in weight played bidirectional roles in both the OS and DFS.

Conclusions: An obesity paradox exists in patients with CRC, with both weight loss and excessive weight gain being detrimental. Patients with CRC may require a reasonable weight management program, and gaining < 5% of the preoperative weight might be an appropriate goal at 6 months after surgery.

1. Introduction

A low body mass index (BMI) and weight loss have been widely confirmed to be associated with a poor prognosis [1,2]. Thus, it is traditionally believed that a high BMI and weight gain lead to better outcomes [3] since a higher body weight provides more nutritional reserves to counteract the negative metabolic consequences of cancer and anticancer treatments [4]. However, emerging evidence

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indicates that obesity is associated with a higher risk of tumor recurrence and death [5–7], and there is an obesity paradox in cancer patients [6–8]. Many leading cancer research organizations are beginning to pay attention to the 'role of obesity in cancer survival and recurrence' [9–12] and are trying to provide weight management recommendations for cancer survivors. However, whether weight gain or loss has an impact on the risk of recurrence and survival remains unclear. Most of the previous research has evaluated only the relationships between the baseline BMI and risk of recurrence and death, and few studies have evaluated the association of the change in weight after diagnosis with the risk of cancer recurrence and death.

Colorectal cancer (CRC) is one of the cancers that are most strongly associated with obesity [13]. There is substantial evidence confirming that obesity can increase the risk of CRC recurrence and death [14]. However, most of these lines of evidence originated from Western countries, where the incidence rates of both obesity and CRC are quite high [15,16]. The incidence rates of obesity and CRC have historically been low in Asian countries, including China [17]. However, with the rapid development of economy and popularity of a Western lifestyle, overweight/obese is becoming a serious public health problem in China, especially in urban populations [18]. Regarding the link between obesity and CRC, the incidence of CRC in China has increased by more than two times in the past three decades, and both the incidence and mortality rates related to CRC in large urban populations are nearly 2 times higher than those in rural populations [19]. The evidence originated from Western countries showed that the BMI cut-off point used for determining the risk of death was approximately 35 kg/m^2 [15,16]. However, a systematic review of 56 observational studies found that the risk of CRC increased sharply in Asians when the BMI exceeded 23 kg/m^2 due to the differences in body composition (BC) between Asian and Western populations [20]. Nevertheless, few studies have focused on the association of obesity with the risk of recurrence of and death related to CRC in Asians, including Chinese individuals.

Thus, whether the obesity paradox exists in the Chinese population and what the most appropriate BMI cut-off point(s) is remain unclear. We conducted this retrospective observational study to evaluate the relationships among the preoperative BMI, change in weight during postoperative chemotherapy and the risk of recurrence and death in patients with stage II-III CRC.

2. Patients and methods

2.1. Study population and design

In this study, a retrospective analysis of 902 patients with CRC who underwent radical colectomy at Peking University Shenzhen Hospital (Shenzhen, China) from January 2012 to December 2017 was conducted, with approval from the Human Research Ethics Committee of Peking University Shenzhen Hospital. The enrolled patients met the following inclusion criteria: 1) were aged $\geq$ 18 years; 2) had an American Society of Anesthesiologists (ASA) score of $\leq$ 3; 3) did not undergo antitumor therapy before surgery; 4) had confirmed cases of stage II or III CRC and was considered to have risk factors that warranted first-line standard postoperative adjuvant chemotherapy regimens based on a postoperative pathology evaluation; 5) had complete medical records before and after surgery, including surgical records, follow-up data, and postoperative chemotherapy records; and 6) had returned to our hospital for a postoperative review within 6 months after surgery. The exclusion criteria were as follows: 1) patients with stage I CRC, who did not need postoperative chemotherapy; 2) patients with stage IV CRC, who had significant differences in tumor-bearing conditions and anti-tumor treatments; 3) a history of emergency surgery, palliative surgery or combined organ resection; 4) a history of reoperation or a hospital stay longer than 3 weeks due to severe postoperative complications such as an intestinal fistula, bleeding, and abdominal infection; 5) a history of incomplete postoperative chemotherapy or any dose or course change in chemotherapy due to severe complications or other reasons; 6) liver metastasis within the past 6 months, as the presence of undiscovered simultaneous liver metastasis before surgery could not be excluded; 7) death within 6 months after surgery due to severe complications or other reasons; 8) death by an accident or suicide; and 9) newly discovered tumors other than CRC during the follow-up.

2.2. Clinical data

The data extracted from the inpatient and outpatient records included demographic data (age, sex, height, weight, BMI, and comorbidities), tumor-specific data [tumor differentiation, location, size, and tumor, node, metastasis (TNM) stage], surgery data [surgical methods, anastomotic methods, number of lymph nodes retrieved, number of metastatic lymph nodes, and severe postoperative complications (within 30 days after surgery)], postoperative chemotherapy data (doses, courses and severe complications), and survival data.

The tumor stage, type of surgical resection and extent of lymph node dissection were determined according to the Chinese CRC treatment guidelines [21]. Postoperative complications were assessed using the Clavien–Dindo classification, with severe complications being defined as grade III or higher [22]. Comorbidities were assessed using the Charlson comorbidity index (CCI) [23]. Metabolic syndrome (MS) components [24], such as diabetes, hypertension, cardio-cerebro-vascular diseases, hyperlipidemia and fatty liver, were also recorded, and the patients were divided into two groups: patients with MS components and patients without MS components.

BMI was calculated by the following formula: BMI (kg/m^2) = weight (kg)/height (m)^2, and patients were divided into four groups according to the standards of the Working Group on Obesity in China (WGOC): underweight, BMI $\leq$ 18.5 kg/m^2; normal weight, 18.5–23.9 kg/m^2; overweight, 24.0–27.9 kg/m^2; and obese, BMI $\geq$ 28.0 kg/m^2 [25]. Our analysis revealed that the results in the overweight and obese categories were consistent, so we combine the overweight and obese categories into one group for simplicity in the subsequent analysis. Thus, the patients were divided into three groups based on their BMI values: underweight, normal weight and overweight/obese.

The preoperative weight and postoperative weight when patients returned to the hospital for review after postoperative chemotherapy (approximately 6 months after surgery) were retrieved from the medical records. The percentage of change in weight was calculated by the following formula: [(postoperative weight - preoperative weight) $\div$ preoperative weight] $\times$ 100%, where negative values indicated weight loss and positive values indicated weight gain. The patients were divided into four groups according to the degree of change in weight: weight gain $\geq$ 5%, maintained weight or weight gain < 5%, weight loss < 5% and weight loss $\geq$ 5%.

2.3. Follow-up

All patients were followed up via inpatient medical visits and telephone interviews. Mortality data, including the time and cause of death, were retrieved for all patients. Overall survival (OS) was defined as the interval between the date of surgery and the date of death. Cancer events (tumor recurrence/metastasis and new CRC

cases in the other colorectal segments) were recorded. However, patients who developed liver metastasis within 6 months were excluded since the presence of undiscovered simultaneous liver metastasis before surgery could not be excluded. Disease-free survival (DFS) was defined as the interval between the date of surgery and the date of the cancer events.

2.4. Statistical analysis

Statistical analyses were performed with SPSS 19.0, the R programming language 2.15.2 and Stata 14.2 SE. The Kolmogorov–Smirnov test was used to evaluate the normality of the data for the variables. The data are expressed as the mean values (± standard deviations) or medians (interquartile ranges), depending on the normality of the data for the variables. The data for different variables were compared among groups using ANOVA or the Kruskal–Wallis test, depending on the normality of the data for the variables. Chi-squared tests were used for categorical variables. Survival curves were estimated using the Kaplan–Meier method and analyzed using the log-rank test. Univariate Cox proportional hazards models of all potential baseline predictors, including sex (men vs women), age, preoperative BMI, change in weight, MS components, CCI, tumor stage, ASA score, type of surgery (open operation vs laparoscopic operation), histological differentiation (high vs moderate vs low differentiation) and histopathological type (tubular adenocarcinoma vs villoglandular, adenocarcinoma vs villous adenocarcinoma), were constructed to compute the hazard ratios (HRs) with their 95% confidence intervals (CIs). Multivariable Cox proportional hazards models were formulated using variables that had significant results in the univariate models. The proportional hazards assumption was verified using the methods published by Grambsch and Therneau [26]. The continuous variables (preoperative BMI and change in weight) were modeled using restricted cubic splines to assess the possible nonlinearity of their effects and to select the appropriate degrees of freedom for subsequent modeling. For each variable and endpoint, three automatically selected knots per model were initially used, with additional knots added as necessitated by visual inspection of the spline plots and formal significance tests. To determine whether the effects of any covariables were dependent on other covariables, partial interaction tests were performed for each variable in the multivariable model, where a statistically significant partial interaction prompted the exploration of its pairwise component interactions. Pairwise interactions were then included in the final models if statistically significant results, according to a likelihood ratio test, were found for both members of the pair. The final models were comprised of all relevant main effects and pairwise interactions, and the fitted models were subsequently used to construct both visual nomograms and online web calculators for the 3-year DFS and 5-year OS probabilities. The final models used for predicting DFS and OS were validated using bootstrapping so that optimism-corrected discrimination could be performed via the concordance index for the survival data; in addition, calibration plots were generated to compare the survival data with the tumor stage. Risk discrimination for the DFS and OS was also performed for the models. Statistical significance was established at $P < 0.05$ (2-sided).

3. Results

3.1. Demographics and disease characteristics of the patients

A total of 1590 patients with stage II or III CRC underwent radical colectomy in our hospital during the study period. Finally, 902 subjects met the inclusion criteria. There were 527 males and 375 females, 217 patients with stage II CRC and 685 patients with stage III CRC, and the mean patient age was 53.7 ± 13.6 years. The demographic characteristics according to the BMI groups are listed in Table 1.

Preoperatively, 11.3% (n = 102) of the patients were underweight, 57.9% (n = 522) were normal weight, 22.8% (n = 206) were overweight and 8.0% (n = 72) were obese. A total of 59.1% (n = 533) of the patients experienced weight loss, and 40.9% (n = 369) maintained their body weight or experienced weight gain, but most patients experienced weight loss or weight gain within 5% of the preoperative weight. The patients with stage III CRC had a lower BMI and lost more weight than did the patients with stage II CRC. The patients who were overweight/obese lost the most weight, and the average percentage change in weight values were 0.19 ± 5.32%, −1.63 ± 5.62% and −3.27 ± 5.56% for the underweight, normal weight, and overweight/obese groups, respectively. There were 344 (38.1%) patients who had MS components. The patients who had MS components had higher rates of overweight/obese (42.2% vs 23.8%) and lost more weight (−2.87 ± 5.55 vs −1.35 ± 5.66) than did those without MS components.

3.2. Analysis of survival differences across groups of patients

During the follow-up period, 488 (54.1%) patients had cancer events (482 had tumor recurrence/metastasis, 6 had new CRC cases in the other colorectal segments), according to the imaging examination, and 174 (19.3%) patients died. Seventy-seven (8.54%) alive patients had only outpatient medical records or oral information confirmed no cancer events, and lacked evidence of imaging examination for more than 1 year from the last follow-up. In order to avoid the undetected cancer events, these patients were not included in subsequent analyses. The median follow-up time for OS was 44 months (range, 19–86 months), and for DFS was 35 months (range, 9–65 months). Thus, we chose to additionally analyze the 3-year DFS and 5-year OS rates. The estimated 3-year DFS and 5-year OS rates among all patients were 62.36% and 68.44%, respectively. In the patients who were underweight, had a normal weight and were overweight/obese, the 3-year DFS rates were 40.90%, 69.58%, and 57.69%, respectively; the 5-year OS rates were 36.01%, 77.38%, and 66.44%, respectively. However, an increased risk of cancer events and death were present in only patients with MS components. Based on the change in weight, the 3-year DFS rates were 37.02%, 57.03%, 86.32% and 79.28% in patients who had weight loss $\geq$ 5%, weight loss < 5%, weight gain < 5% and weight gain $\geq$ 5%, respectively, and the 5-year OS rates were 46.44%, 64.63%, 83.81% and 78.99%, respectively. There were no significant differences in the 3-year DFS ($P = 0.108$) or 5-year OS ($P = 0.122$) between patients with weight gain $\geq$ 5% and weight gain < 5% (Fig. 1).

3.3. The restricted cubic spline models

In the overall sample, the association between the preoperative BMI and both the risk of cancer events and risk of death exhibited U-shaped curves. The inflection point was at 24 kg/m^2 for the risk of cancer events and 25 kg/m^2 for the risk of death. The association between the change in weight and risk of cancer events was nearly linear. The association between the change in weight and risk of death exhibited a U-shaped curve, and the inflection point was 3%. In the subgroup analysis, the association between the preoperative BMI and risk of cancer events exhibited a J-shaped curve in patients with stage II CRC, and the inflection point was at 24 kg/m^2; it exhibited a U-shaped curve in patients with stage III CRC, and the inflection point was at 24 kg/m^2. The association between the change in weight and risk of death exhibited a U-shaped curve in patients with stage II CRC, and the inflection point was 0%; it exhibited an L-shaped curve in patients with stage III CRC, and the inflection point was at 1% (Fig. 2).

Table 1
Demographics and disease characteristics of the patients.

	Underweight	Normal weight	Overweight/Obese	*P* value
Numbers, n	102	522	278	
Ages, $\bar{x} \pm s$, y	47.43 ± 14.97	54.18 ± 13.7	55.12 ± 12.37	<0.001[d]
Sex, n/%				
females	82/80.4%	222/42.5%	71/25.5%	<0.001[f]
males	20/19.6%	300/57.5%	207/74.5%	
BMI, $\bar{x} \pm s$, kg/m^2	17.75 ± 0.51	21.59 ± 1.51	26.7 ± 2.09	<0.001[d]
Change in weight, $\bar{x} \pm s$, ratio	0.19 ± 5.32	−1.63 ± 5.62	−3.27 ± 5.56	<0.001[d]
CCI, median (IQR), score	2 (2/4)	4 (2/5)	4 (2/5)	<0.001[e]
MS, n/%				
yes	16/15.7%	183/35.1%	145/52.2%	<0.001[f]
no	86/84.3%	339/64.9%	133/47.8%	
MS components, n/%				
fatty liver	2/2.0%	14/2.7%	16/5.8%	
cardio-cerebro-vascular diseases	4/3.9%	13/2.5%	15/5.4%	
hypertension	4/3.9%	48/9.2%	42/15.1%	
hyperlipidemia	2/2.0%	61/11.7%	44/15.8%	
diabetes	7/6.9%	69/13.2%	56/20.1%	
ASA, median (IQR), score	1 (1/2)	1 (1/2)	2 (1/2)	<0.001[e]
Tumor stage, n/%				
II	17/16.7%	124/23.8%	76/27.3%	0.095[f]
III	85/83.3%	398/76.2%	202/72.7%	
Survival status, n/%				
alive	62/60.8%	452/86.6%	214/77%	<0.001[f]
dead	40/39.2%	70/13.4%	64/23%	
[a]Cancer events, n/%				
no	23/22.6%	230/44.1%	84/30.2%	<0.001[f]
yes	76/74.5%	246/47.1%	166/59.7%	
uncertain	3/2.9%	46/8.8%	28/10.1%	
Tumor site, n/%				
left colon	65/63.7%	225/44.1%	83/29.9%	<0.001[f]
right colon	37/36.3%	285/55.9%	195/70.1%	
[b]Degree of differentiation, n/%				
high	14/13.7%	96/18.4%	66/23.7%	0.013[g]
moderate	84/82.4%	367/70.3%	174/62.6%	
low	4/3.9%	51/9.8%	38/13.7%	
undetermined	0/0%	8/1.5%	0/0%	
[c]Histopathological type, n/%				
TA	12/11.8%	30/5.7%	29/10.4%	0.031[g]
VGA	69/67.6%	334/64.0%	168/60.4%	
VA	21/20.6%	153/29.3%	81/29.1%	
special types	0/0%	5/1%	0/0%	
Surgical approach, n/%				
laparoscopic operation	69/67.6%	265/50.8%	105/37.8%	<0.001[f]
open operation	33/32.4%	257/49.2%	173/62.2%	

BMI: body mass index; $\bar{x} \pm s$: mean value (± standard deviation); IQR: interquartile range; Change in weight was calculated by the following formula: [(postoperative weight - preoperative weight) ÷ preoperative weight] × 100%, where the negative values indicate weight loss and positive values indicate weight gain; CCI: Charlson comorbidity index; MS: metabolic syndrome, the total frequency of MS components were more than the numbers of patients with MS, since some patients had multiple MS components; ASA: American Society of Anesthesiologists; TA: tubular adenocarcinoma; VGA: villoglandular adenocarcinoma; VA: villous adenocarcinoma.

[a] There were 3, 46 and 28 patients in underweight, normal weight and overweight/obese group respectively who's cancer events were uncertain.
[b] The degree of differentiation were undetermined in 8 patients in normal weight group.
[c] There were 5 patients with special pathological types of CRC in normal weight group.
[d] ANOVA test.
[e] Kruskal–Wallis test.
[f] Chi square test.
[g] Fisher exact test.

3.4. Analysis of prognostic factors for the patients

The univariate analysis showed that age, preoperative BMI, change in weight, tumor stage, CCI, and histopathological type were significantly related to poorer 3-year DFS and 5-year OS rates ($P < 0.05$), while the sex, ASA score, tumor site and surgical approach were not associated with either the 3-year DFS or 5-year OS. The CCI is composed of an age score and complication score (most of the complications are MS components). Thus, we included the CCI as a combined factor of age and MS components in the final model for simplicity in the modeling and prognostic evaluation. By default, for Cox proportional hazards models, continuous variable is considered to have a linear trend, whereas the results of the Kaplan–Meier and restricted cubic spline model analyses suggested that the preoperative BMI and change in weight might have bidirectional roles. Therefore, we included both BMI and change in weight as classification variables in the final models.

The significant factors in the multivariable models were identified by the examination of spline plots and HRs across subgroups for continuous and categorical variables, respectively. The final multivariable models and corresponding nomograms for OS and DFS are presented in Figs. 3 and 4, respectively. The relative importance of the variables can be easily inferred from Figs. 3 and 4; for example, the CCI had the largest impact on the OS and DFS risk, followed by the change in weight, preoperative BMI and tumor stage, while the histopathological type had the smallest impact.

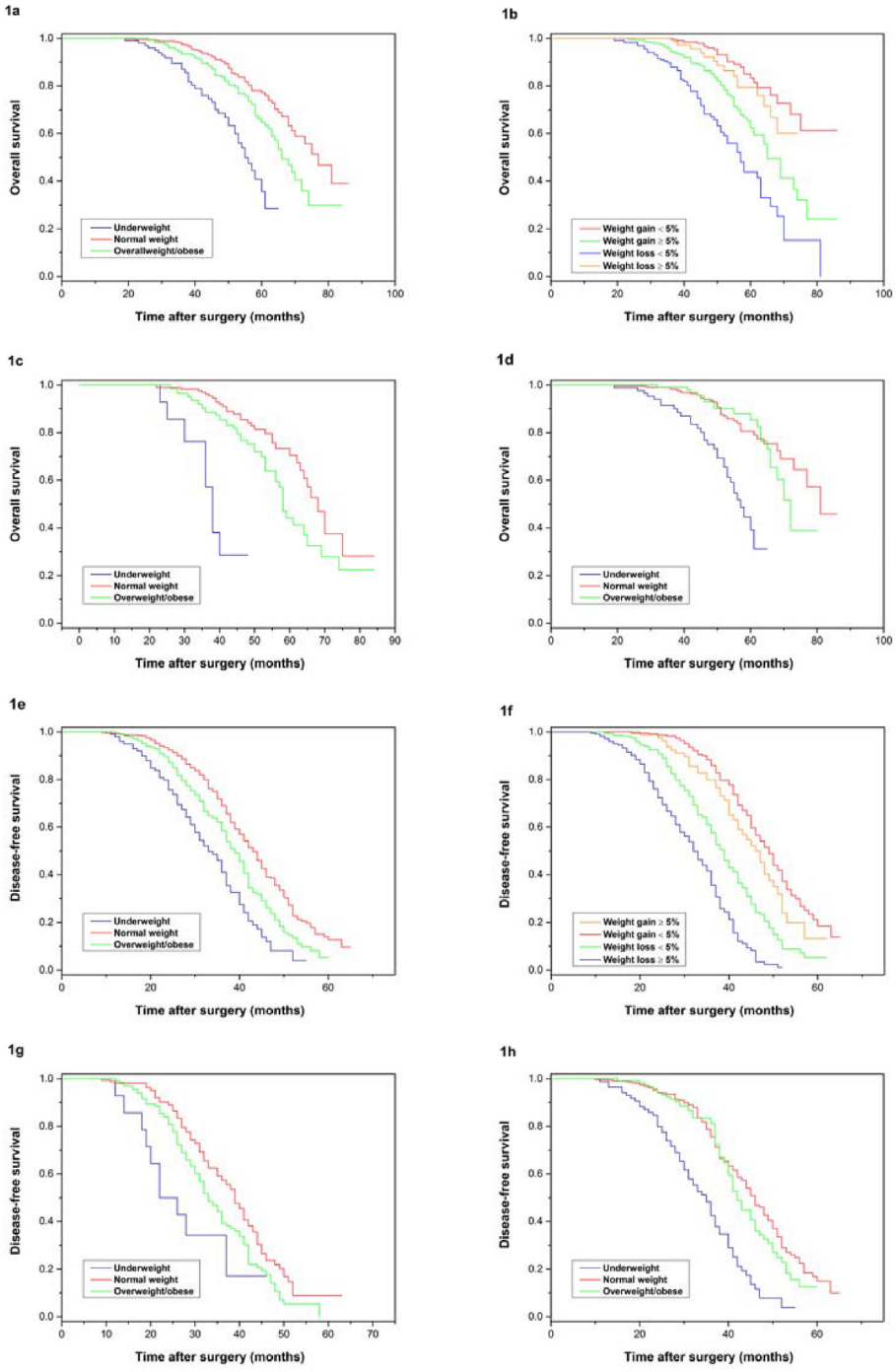

Fig. 1. Kaplan–Meier curves for overall survival (OS) and disease-free survival (DFS). 1a. The OS for the groups created on the basis of the preoperative body mass index (BMI); 1b The OS for the groups created on the basis of the change in weight during the six months after surgery; 1c The OS in patients who had metabolic syndrome (MS) components, stratified by preoperative BMI; 1d The OS in patients who did not have MS components, stratified by preoperative BMI; 1e The DFS in groups divided by the preoperative BMI; 1f The DFS in groups divided by the change in weight; 1g The DFS in patients who had MS components, stratified by the preoperative BMI; 1h The DFS in patients who did not have MS components, stratified by the preoperative BMI.

The preoperative BMI and change in weight play bidirectional roles; the group of patients who were underweight and had weight loss had the highest risk of cancer events and death, the group of patients with a normal weight and weight gain < 5% had the lowest risk, and the group that were overweight/obese and had weight gain ≥ 5% had a poorer prognosis than did those with a normal weight and weight gain < 5%. Compared with the underweight group, the normal weight (HR 0.17, 95% CI 0.12–0.22) and overweight/obese (HR 0.24, 95% CI 0.18–0.33) groups had a better 3-year DFS rates. Moreover, compared with the group of patients who had weight loss ≥5%, the groups with weight loss < 5% (HR 0.39, 95% CI 0.31–0.50), weight gain < 5% (HR 0.12, 95% CI 0.09–0.16) and weight gain ≥5% (HR 0.19, 95% CI 0.13–0.27) had better 3-year DFS rates ($P < 0.001$). Compared with being underweight, being at a normal weight (HR 0.098, 95% CI 0.061–0.16) or overweight/obese (HR 0.122, 95% CI 0.075–0.20) had a protective

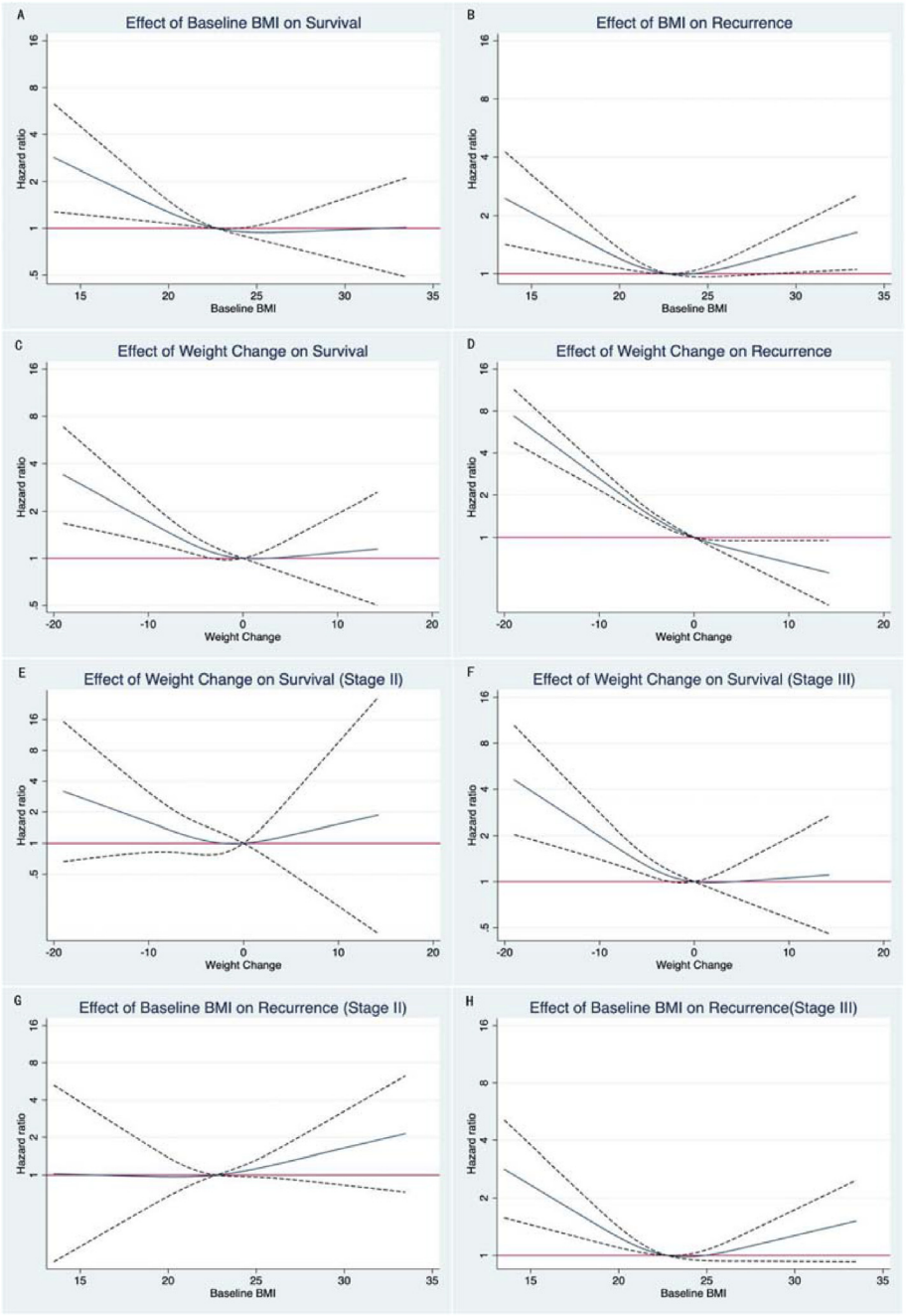

Fig. 2. Risk of death (on the log hazard ratio scale, y-axis) as a function of (A) the preoperative body mass index (BMI) and (C) change in weight. The risk of cancer events as a function of (B) the preoperative BMI and (D) change in weight. The risk of death as a function of (E and F) the change in weight in patients with stage II and III CRC. The risk of recurrence as a function of (G and H) the preoperative BMI in patients with stage II and III CRC. Solid line = risk function. Dashed lines = 95% confidence bands for the risk function.

effect; compared with the group of patients who had weight loss $\geq$ 5%, the groups with weight loss < 5% (HR 0.336, 95% CI 0.228–0.50), weight gain < 5% (HR 0.093, 95% CI 0.054–0.16) and weight gain $\geq$5% (HR 0.181, 95% CI 0.099–0.33) had better 5-year OS rates.

3.5. Predictive value according to our final multivariable model

The concordance index values of C for DFS and OS according to our final model were 0.822 (range, 0.803–0.840) and 0.845 (range, 0.817–0.874), respectively. Thus, our final model had high predictive ability (Fig. 5).

4. Discussion

Our study found that an obesity paradox exists in Chinese patients with CRC, the association between the preoperative BMI and both the risk of cancer events and death exhibit U-shaped curves, and the individuals who have a normal weight have the most favorable DFS and OS rates. There are many possible explanations for the obesity paradox.

Emerging evidence suggests that excessive adipose tissue leads to the excessive release of free fatty acids and the secretion of adipocytokines and proinflammatory cytokines, which lead to insulin resistance (IR) and systemic inflammatory response

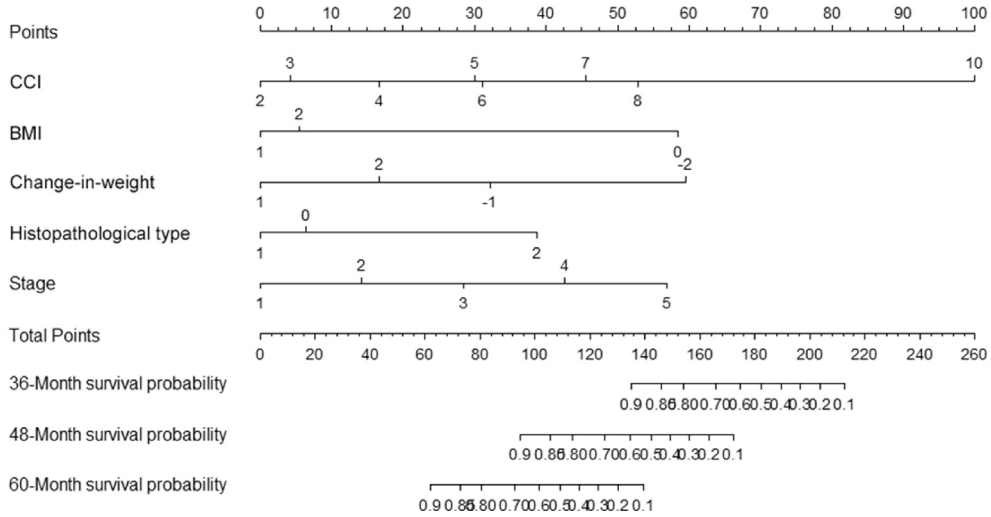

Fig. 3. A nomogram for overall survival (OS). An example patient's predictions may be obtained from a single nomogram as follows. First, the risk points associated with each variable are obtained via the vertical translation of the patient's variable value (e.g., the 'change in weight') to the scale labeled 'Points' in the nomogram (i.e., weight loss = −2 contributes 60 points to OS risk). Next, the points associated with each variable value for the patient are totaled across all variables. This total is located on the scale 'Total Points' (e.g., 140 for OS) and then vertically mapped to obtain the prediction of interest (i.e., five-year OS probability of 10%). BMI: body mass index: underweight (0 points), normal weight (1 point), overweight/obese (2 points); change in weight: weight loss ≥ 5% (−2 points), weight loss < 5% (−1 point), weight gain < 5% (1 point) and weight gain ≥ 5% (2 points); tumor stage: stage IIA (1 point), IIB (2 points), IIIA (3 points), IIIB (4 points), IIIC (5 points); CCI: Charlson comorbidity index; histopathological type: tubular adenocarcinoma (0 points), villoglandular adenocarcinoma (1 point), villous adenocarcinoma (2 points); OS: overall survival.

syndrome (SIRS); these conditions have been widely indicated to stimulate cancer cell growth, invasion and metastasis [27–29]. Thus, fat mass may play a bidirectional role in cancer patients [30–32]. An appropriate level of fat mass can provide necessary nutritional reserves, while excessive adipose tissue may promote cancer recurrence and death [33]. Patients who have a normal weight are more likely to have adequate muscle and fat masses; thus, they have the most favorable outcomes. Patients who are overweight and obese might have an increased risk of recurrence and death because they have an excessively high fat mass [2,33]. Furthermore, many studies have demonstrated that IR and SIRS are the co-mechanisms between obesity and an increased risk of MS and cancer [34]. Of note, Yamaji et al. found that the association between obesity and an increased risk of CRC was present in only subjects who had obesity-related MS, suggesting that metabolic abnormalities may play a crucial role in the risk of CRC [35]. We found similar results showing that an increased risk of cancer events and death were present in only patients with MS components. The CCI, which is mainly composed of MS components, had the largest impact on cancer events and death.

In regard to the obesity paradox in cancer patients, selection bias has to be considered [32,36]. In patients with advanced cancer, who are at a high risk of malnutrition, a higher BMI and necessary nutritional reserves may lead to better outcomes [37]. However, in patients with earlier stages of the disease, who have a low risk of malnutrition and a long life expectancy, an excessively high fat mass may lead to shorter survival due to the increased risk of recurrence [36]. However, we found that the relationship between

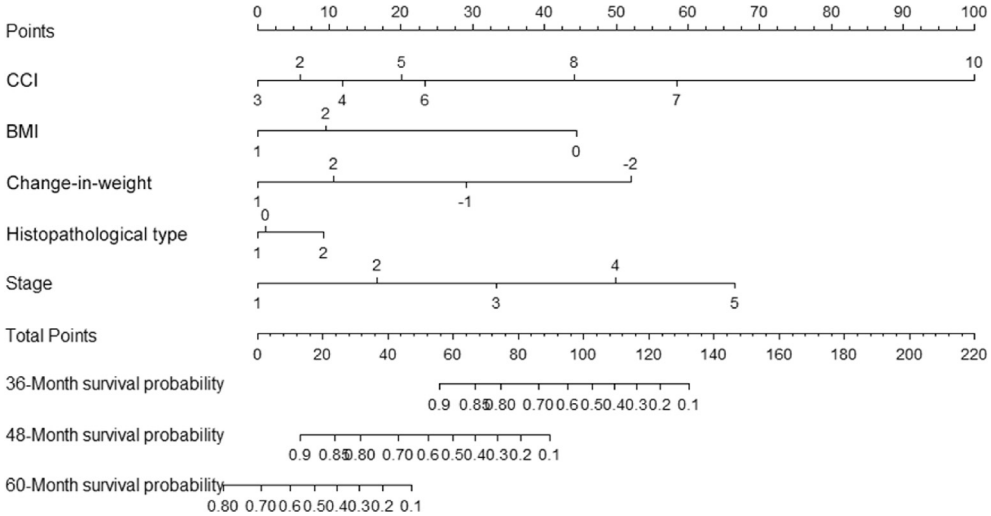

Fig. 4. A nomogram for disease-free survival (DFS). The nomogram is used as described in the legend for Fig. 3. BMI: body mass index, underweight (0 points), normal weight (1 point), overweight/obese (2 points); change in weight: weight loss ≥ 5% (−2 points), weight loss < 5% (−1 point), weight gain < 5% (1 point) and weight gain ≥5% (2 points); tumor stage: stage IIA (1 point), IIB (2 points), IIIA (3 points), IIIB (4 points), IIIC (5 points); CCI: Charlson comorbidity index; histopathological type: tubular adenocarcinoma (0 points), villoglandular adenocarcinoma (1 point), villous adenocarcinoma (2 points); DFS: disease-free survival.

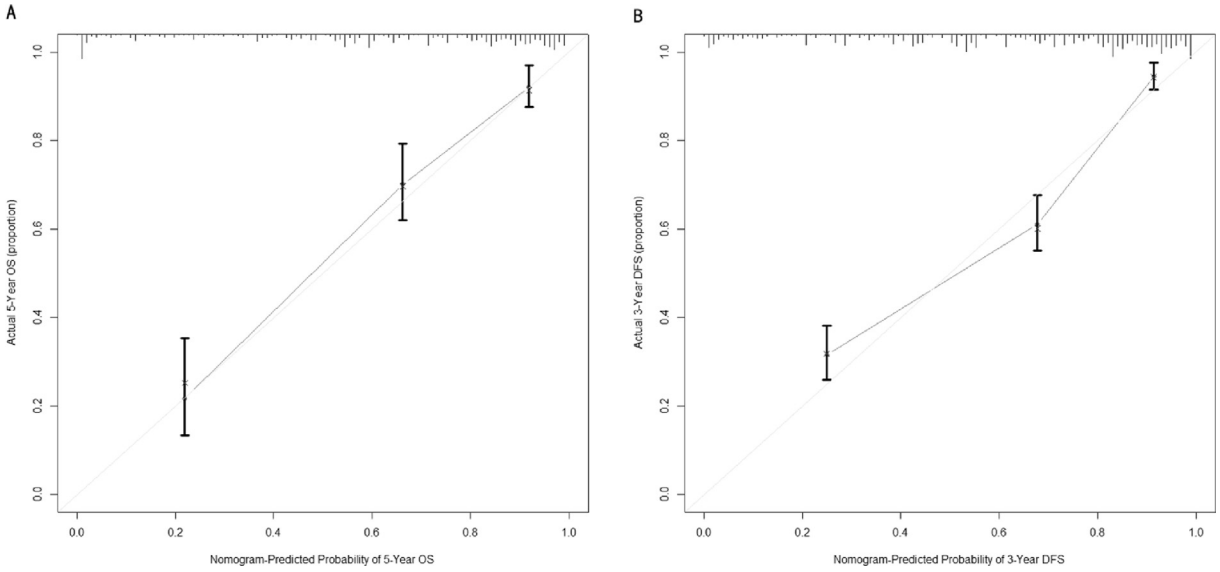

Fig. 5. Calibration curves for the final multivariable model for the nomogram predictions of the 5-year overall survival (A) and 3-year disease-free survival (B). The dashed lines indicate an ideal nomogram; the solid lines indicate the developed nomogram; the vertical bars show the 95% CIs.

the preoperative BMI and risk of cancer events and death exhibited U-shaped curves in patients with both stage II and III CRC.

It is currently unclear whether there is a direct or an inverse causal relationship between underweight and risk of recurrence of and death. The increasing levels of proinflammatory and procachectic factors in patients with cancer may trigger both tumor progression and weight loss [38]. Thus, underweight may indicate not only a lack of nutritional reserves but may also reflect the increased metabolic activity of a more aggressive tumor biology, which would lead to poorer outcomes [39]. This feature may be more pronounced in patients with advanced tumors. Our results showed that underweight had a larger effect on the risk of cancer events in patients with stage III CRC. The association between preoperative BMI and risk of cancer events exhibited a U-shaped curve in patients with stage III CRC and a J-shaped curve in patients with stage II CRC.

Ethnic differences must also be taken into account. In studies conducted in Western countries, the most favorable outcomes occurred in individuals who had a BMI ranging from 25 to 35 kg/m^2, and the BMI cut-off point used for determining the point at which the risk of death increased was approximately 35 kg/m^2 [15,16]. However, the East Asians have higher visceral fat mass for a given BMI due to their lower muscle mass and tendency toward having abdominal distribution of fat [40]. Ning Y et al. found that the risk of CRC increased sharply in Asians when the BMI exceeded 23 kg/m^2 [20]. Our results showed similar results: the inflection point was at 24 kg/m^2 for the risk of cancer events and 25 kg/m^2 for the risk of death in Chinese CRC patients.

There are great differences in BC between men and women, and such differences might alter the association between obese and risk of cancer events and death. Some studies found that the obesity paradox was more pronounced in men [5,13,32], while others held the opposite views [30,41]. However, we found a consistent association among the preoperative BMI and the risk of cancer events and death between men and women.

We analyzed the association between the change in weight and the risk of cancer events and death. It should be noted that weight loss during postoperative chemotherapy might have been mainly caused by gastrointestinal dysfunction after surgery and side effects of chemotherapy. Furthermore, weight loss $\geq$ 2% within 6 months is considered to be a risk factor for malnutrition [42]. Therefore, the association between weight loss and the risk of cancer events and death in this study mainly reflected the effects of malnutrition during postoperative chemotherapy rather than weight control achieved in asymptomatic patients after antitumor treatments via dietary and exercise-related interventions. Therefore, we found that weight loss was always an adverse factor. However, we found that patients with weight gain $\geq$5% had a higher risk of cancer events and death than did patients with weight gain < 5%. These results are consistent with those of a study by Thivat E et al. in patients with breast cancer during postoperative chemotherapy [43]. However, the association between change in weight and risk of death exhibited an L-shaped curve in patients with stage III CRC, suggesting that weight gain might mainly play a protective role in these patients.

Thus, any advice on weight management for cancer patients must be given with caution. Plus, the evidence from current randomized clinical trials (RCTs) is not yet available [44]. Studies failed to confirm their hypotheses due to poor patient compliance. Most of the patients followed interventions lasting less than 6 months [45–47]. We believe that patients have poor compliance with weight control programs is due to a lack of strong evidence that indicates a change in weight does affect the risk of recurrence and death. While the present results may be insufficient to change clinical practice, they do provide new evidence that may help improve patient compliance in future RCTs.

Our current study has substantial strengths. First, we simultaneously evaluated the effects of the baseline BMI and change in weight after surgery on the risk of cancer events and death and found that obesity and excessive weight gain were not always beneficial. Second, we retrieved BMI and change in weight data from the hospital records and excluded patients who had severe postoperative complications and patients who underwent incomplete postoperative chemotherapy; thus, the confounding factors of postoperative complications and incomplete chemotherapy, as well as recall bias of BMI and weight change, were excluded. The results therefore provided specific and strong evidence of such associations. Nevertheless, there are several limitations that must be noted. First, our study was a retrospective observational study, so causal relationships cannot be inferred. Second, as in all observational studies, there is a possibility that some confounding factors

were not measured. However, our results were robust to adjustments for numerous potential confounding variables.

5. Conclusion

Our results showed that the lowest risk of cancer events and death were in those who had a normal weight and had weight gain < 5% during the 6 months after surgery; patients who were underweight or overweight/obese and had weight loss or weight gain ≥ 5% had a poorer prognosis. These results support the existence of an obesity paradox and demonstrate that weight gain is not always beneficial. Cancer patients may need a reasonable weight management program, and according to our results, maintaining the preoperative weight or gaining < 5% of the preoperative weight might be an appropriate range at 6 months after surgery.

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Authors' contributions

Chunlei Hu, Xinghan Jin and Yiming Zhang contributed to data collection; Qi Zhang and Lin Zhang performed statistical analysis; Chunlei Hu, Qiankun Zhu and Meng Tang wrote this paper; Hanping Shi was the chief of this study and 2017YFC1309200; and Lyv GQ was the chief of SZSM201612051.

Conflict of interest

The authors have no disclosure of interest regarding this article.

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