

ORIGINAL ARTICLE

Prognostic significance of the pN classification supplemented by body mass index for esophageal squamous cell carcinoma

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Abstract

Background: Body mass index (BMI) has been associated with the risk of esophageal cancer. But the influence of BMI on postoperative complications and prognosis has always been controversial.

Methods: Between 2000 and 2007, 424 patients with esophageal squamous cell carcinoma (ESCC) underwent R0 esophagectomy at our center without neoadjuvant therapy. We performed univariate and multivariate analyses to identify prognostic factors for survival.

Results: Patients were divided into three groups according to Asian-specific BMI cut-off value: underweight (n = 45), normal weight (n = 228), and overweight and obese (n = 151). Mean follow-up time was 39 months. The five-year overall survival (OS) rate was 19%, 34%, and 42% for underweight, normal weight, and overweight and obese, respectively ($P < 0.001$). The five-year disease-free survival (DFS) rate was 24%, 41%, and 74% for underweight, normal weight, and overweight and obese, respectively ($P < 0.001$). Multivariate analysis showed that pT, pN, and BMI were independent prognostic factors for DFS and OS. The C-index to the combined model showed improved predictive ability when compared to the pN classification (0.779 vs. 0.734).

Conclusion: Preoperative BMI was an independent prognostic factor for OS and DFS. The proposed new prognostic model with the pN classification supplemented by BMI might improve the ability to discriminate ESCC patients' outcome.

Introduction

Esophageal cancer is one of the most common cancers in the world, with 480 000 new cases and 400 000 deaths annually, of which about half occurred in China.¹ As the dominant type of esophageal cancer in China, esophageal squamous cell carcinoma (ESCC) is generally accompanied by a poor prognosis because of the lack of a single effective clinical method for early diagnosis. Despite advances in surgical techniques and the incorporation of new therapeutic approaches, the outcome for patients with ESCC remains poor, with a five-year overall survival (OS) rate of 15–34%.^{2–4}

There is strong evidence that lifestyle factors, such as physical activity, diet, and obesity may have an effect on survival for some cancers.⁵ During the last few decades, the proportion of overweight esophageal cancer patients has been rising. An association between body mass index (BMI) and risk of esophageal cancer has been established.^{6–9} However, there is no general consensus on the influence of BMI on survival in esophageal cancer patients. Some studies have suggested that patients with a higher BMI had a significantly better prognosis than those with a lower BMI, whereas others yielded conflicting results.^{9–20} Although the tumor node metastasis (TNM) system has effective parameters to predict the

prognosis of patients with ESCC, discrepancy in prognosis within the same stage has always existed.²¹ Therefore, there is an urgent demand for new parameters in risk stratification to complement TNM staging in order to instruct individualized treatment.

Materials and methods

Patients

All ESCC patients who underwent radical esophagectomy at the Sun Yat-sen University Cancer Center between October 2000 and May 2007 were included in this study. Selective criteria included: (i) patients did not undergo neoadjuvant treatment; (ii) complete resection of the tumor; (iii) the incised margin was negative; and (iv) no distant metastasis was present. We collected clinicopathological data including patient age, gender, tumor location, tumor size, tumor differentiation, pTNM stage (7th edition), lymph node status, and BMI. These data are detailed in Table 1. Relapse was consid-

ered from the date of surgery to the first recurrence or metastasis. The ethics committee of the Sun Yat-sen University Cancer Center approved the study.

Body mass index (BMI)

Body mass index (kg/m^2) was calculated based on a direct measurement of height and weight at diagnosis. Patients were classified according to Asian-specific BMI cut-off values as follows: underweight ($<18.5 \text{ kg}/\text{m}^2$); normal weight ($18.5\text{--}22.9 \text{ kg}/\text{m}^2$) (reference group); and overweight and obese ($\geq 23.0 \text{ kg}/\text{m}^2$). These values were chosen because evidence exists that an excess risk of mortality from all causes occurs at lower BMI levels in Asians than in Caucasians.²² The mean BMI of the Chinese population is relatively low.¹⁰

Statistical analysis

The correlation between BMI and the clinicopathologic features of the ESCC patients was evaluated by a χ^2 -test. For

Table 1 Correlation of BMI with patients' clinicopathological features in primary esophageal squamous cell carcinomas

Variables	BMI				P value*
	Cases	<18.5 kg/m ² (underweight)	18.5–22.9 kg/m ² (normal weight)	≥23.0 kg/m ² (overweight and obese)	
Age (years)					0.648
≤57.0†	223	26 (11.7%)	123 (55.2%)	74 (33.2%)	
>57.0	201	27 (13.4%)	102 (52.7%)	72 (35.8%)	
Gender					0.193
Female	109	13 (11.9%)	53 (48.6%)	43 (39.4)	
Male	315	40 (12.7%)	172 (54.6%)	103 (32.7)	
Location					0.945
Upper	26	4 (15.4%)	15 (57.7%)	7 (26.9%)	
Middle	292	36 (12.3%)	154 (52.7%)	102 (34.9%)	
Lower	106	13 (12.3)	56 (52.8%)	37 (34.9%)	
Tumor size (cm)					0.456
≤4‡	271	30 (11.1%)	148 (54.6%)	93 (34.3%)	
>4	153	23 (15%)	77 (50.3%)	53 (34.6%)	
Differentiation					0.188
Well	66	7 (10.6%)	29 (43.9%)	30 (45.5%)	
Moderate	281	39 (13.9%)	155 (55.2%)	87 (31%)	
Poor	77	7 (9.1%)	41 (53.2%)	29 (37.7%)	
pT status					0.232
T1	20	5 (25%)	9 (45.0%)	6 (30%)	
T2	102	8 (7.8%)	60 (58.8%)	34 (33.3%)	
T3	302	40 (13.2%)	156 (51.7%)	106 (35.1%)	
pN status					0.806
N0	230	29 (12.6%)	122 (53%)	79 (34.3%)	
N1	109	14 (12.8%)	63 (57.8%)	32 (29.4%)	
N2	68	8 (11.8%)	32 (47.1%)	28 (41.2%)	
N3	17	2 (11.8%)	8 (47.1%)	7 (41.2%)	
Stage					0.239
I	25	6 (24%)	9 (36.0%)	10 (40%)	
II	234	25 (10.7%)	131 (56.0%)	78 (33.3%)	
III	165	22 (13.3%)	85 (51.5%)	58 (35.2%)	

*Chi-square test. †Median age. ‡Median size. BMI, body mass index.

univariate analysis, survival curves were obtained with the Kaplan–Meier method, and the differences in survival between groups was tested by log-rank test. Multivariate survival analyses were performed with the Cox proportional hazard regression model. The primary endpoint was OS, which was calculated from the time of surgery to the time of death from any cause. The second endpoints were postoperative complications and disease-free survival (DFS). DFS was calculated from the time of surgery to the first recurrence of cancer or death from any cause. The Harrell concordance index (C-index) was employed to assess model prognostic accuracy on multivariate analysis. A significant difference was deemed if the *P* value from a two-tailed test was less than 0.05. Statistical analysis was performed with SPSS statistical software package (SPSS Standard version 19.0; SPSS, Chicago, IL, USA) and R, version 3.0.1.

Results

Four hundred and twenty-four consecutive esophageal cancer patients were included in the study and were divided into three groups according to BMI. Patient characteristics are shown in Table 1.

Univariate and multivariate analysis

Patients with a lower BMI displayed a poorer OS (Table 2; Fig 1a) and DFS (Fig 1b) than patients with a high BMI (*P* = 0.015). Of the other prognostic factors, univariate analysis showed that gender (*P* = 0.028), location (*P* = 0.008), differentiation (*P* = 0.023), pT status (*P* = 0.002), pN status (*P* < 0.0001), stage (*P* < 0.0001), and BMI (*P* = 0.015) affected patient OS (Table 2).

Our results demonstrated that BMI was identified as a prognostic predictor of OS and DFS in ESCC patients without lymph node metastasis (Fig 2). Because variables examined to have prognostic influence by univariate analysis may covariate, the BMI, as well as other clinicopathologic features (including gender, tumor size, differentiation, pT status, pN status, and stage) were tested in multivariate analysis (Table 3). BMI was found to be a significantly independent prognostic factor for poor OS (hazard ratio, 0.698; 95% confidence interval [CI], 0.573–0.851; *P* < 0.001; Table 3). Of the other parameters, pN classification was evaluated as an independent prognostic factor for patient survival. Preoperative BMI was an independent prognostic factor for OS and DFS. The proposed new prognostic model including the pN classification supplemented by BMI might improve the ability to discriminate ESCC patient outcome.

New prognostic model with pN classification supplemented by BMI

According to the results of our multivariate analyses, we proposed a new clinical prognostic model with two prognostic

Table 2 Univariate analysis of BMI and clinical variables in patients with primary esophageal squamous cell carcinoma (log-rank test)

Variables	Cases	Mean survival (months)	Median survival (months)	<i>P</i> value
Age (years)				0.596
≤57.0*	223	62.6	45.0	
>57.0	201	60.5	63.0	
Gender				0.028
Female	109	72.2	NR	
Male	315	58.2	41.0	
Location				0.008
Upper	26	71.6	79.0	
Middle	292	56.4	41.0	
Lower	16	70.4	63.0	
Tumor size (cm)				0.057
≤4†	271	66.1	64.0	
	153	54.1	33.0	
Differentiation				0.023
Well	66	61.2	55	
Moderate	281	66.0	68.0	
Poor	77	44.5	26.0	
pT status				0.002
T1	20	58.2	NR	
T2	102	71.2	74.0	
T3	302	58.2	39.0	
pN status				<0.0001
N0	230	79.5	NR	
N1	109	47.8	40.0	
N2	68	27.4	16.0	
N3	17	20.1	11.0	
Stage				<0.0001
I	25	67.6	NR	
II	234	76.8	NR	
III	165	34.9	21.0	
BMI				0.015
<18.5 kg/m ²	53	47.4	24.0	
18.5–22.9 kg/m ²	225	61.0	41.0	
≥22.9 kg/m ²	146	59.5	74.0	

*Median age. †Median size. NR indicates not reached. BMI, body mass index.

Table 3 Cox multivariate analyses of prognostic factors on overall survival

Variables	Hazard ratio	95% CI	<i>P</i> value
Gender (female vs. male)	0.779	0.564–1.891	1.074
Size (≤4 cm vs. >4 cm)	1.095	0.834–1.438	0.531
pT status (T1 vs. T2 vs. T3)	1.146	0.831–1.579	0.406
pN status (N0 vs. N1 vs. N2 vs. N3)	1.687	1.339–2.125	<0.0001
Stage (I vs. II vs. III)	1.131	0.728–1.757	0.583
Grade (well vs. moderate vs. poor)	1.114	0.887–1.398	0.352
BMI (<18.5 kg/m ² vs. 18.5–22.9 kg/m ² vs. ≥22.9 kg/m ²)	0.698	0.573–0.851	<0.001

*Median size. BMI, body mass index; CI, confidence interval.

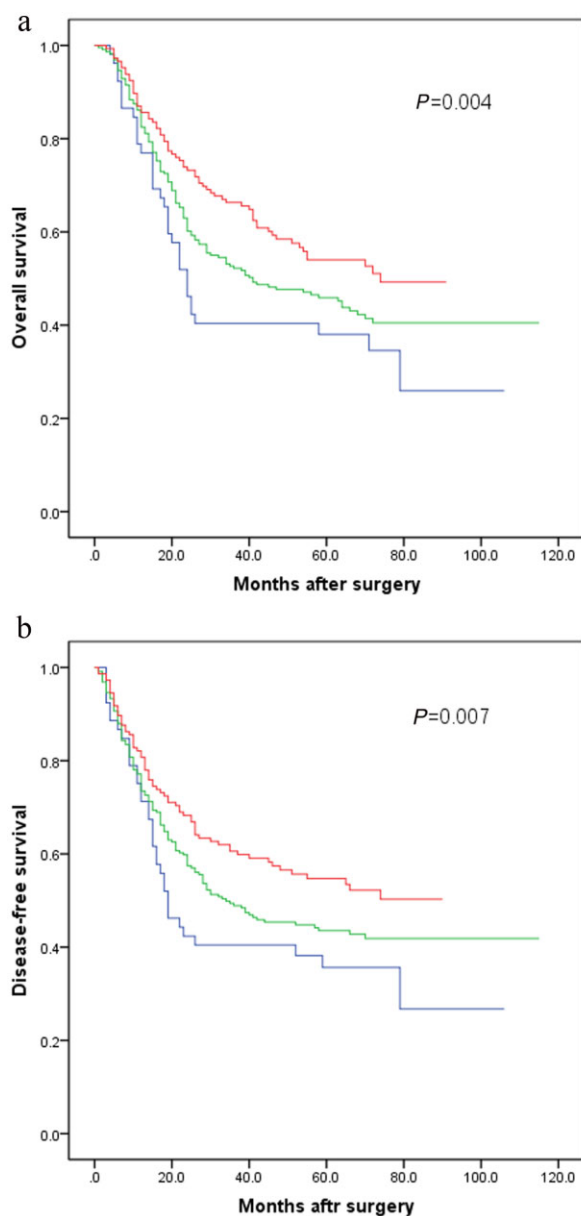


Figure 1 The association of body mass index (BMI) with esophageal squamous cell carcinoma (ESCC) patients' survival (log-rank test). Kaplan-Meier survival analysis of BMI for (a) overall survival, and (b) disease-free survival. —, BMI ≤ 18.5 ; —, $18.5 < \text{BMI} < 23$; —, BMI ≥ 23 .

factors: pN classification and BMI. We designated three groups: a high-risk group including the advanced pN classification (2 or 3) and a lower BMI ($<23 \text{ kg/m}^2$); an intermediate risk group including either the advanced pN classification (2 or 3) or lower BMI ($<23 \text{ kg/m}^2$); and a low-risk group without these factors. Our results revealed that the proposed model could significantly stratify the risk (low, intermediate, and high) for OS (Fig 3a, $P=0.004$) and DFS (Fig 3b $P=0.002$). Application of the C-index to the proposed new prognostic

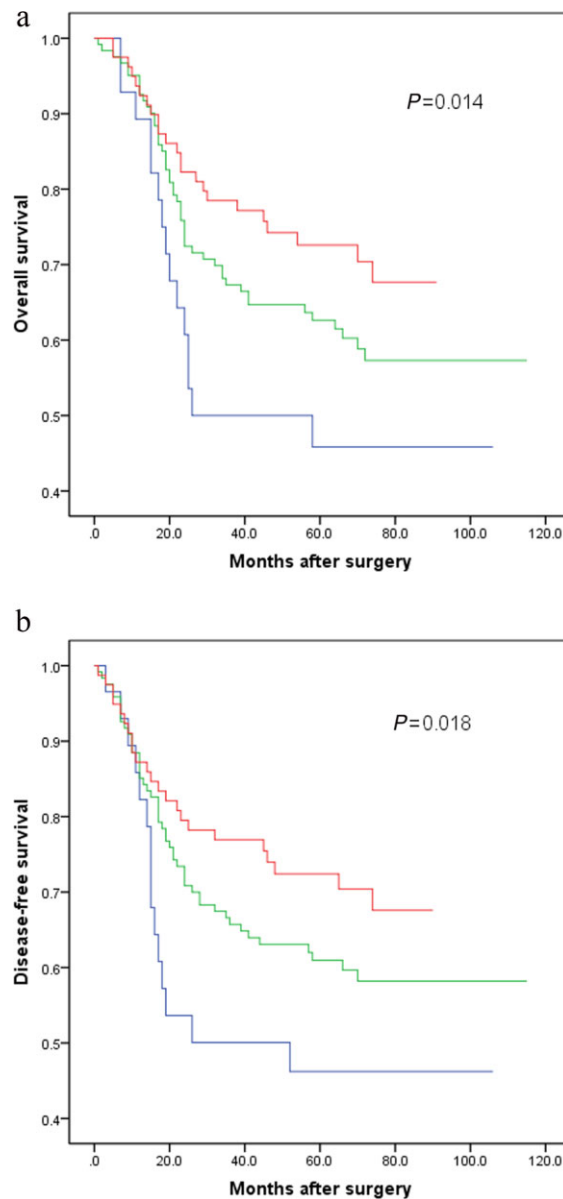


Figure 2 Univariate survival analysis with regard to body mass index (BMI) in the subset of esophageal squamous cell carcinoma ESCC patients with pN0 classification. The BMI was identified as a prognostic predictor of overall survival (a) and recurrence-free survival (b) in ESCC patients without lymph node. —, BMI ≤ 18.5 ; —, $18.5 < \text{BMI} < 23$; —, BMI ≥ 23 .

model showed improved predictive ability when compared with the single pN classification model (0.779 vs. 0.734, $P < 0.05$).

Discussion

In this relatively large cohort of patients with ESCC who underwent esophagectomy with a long-term postoperative follow-up, we found that BMI was independently and

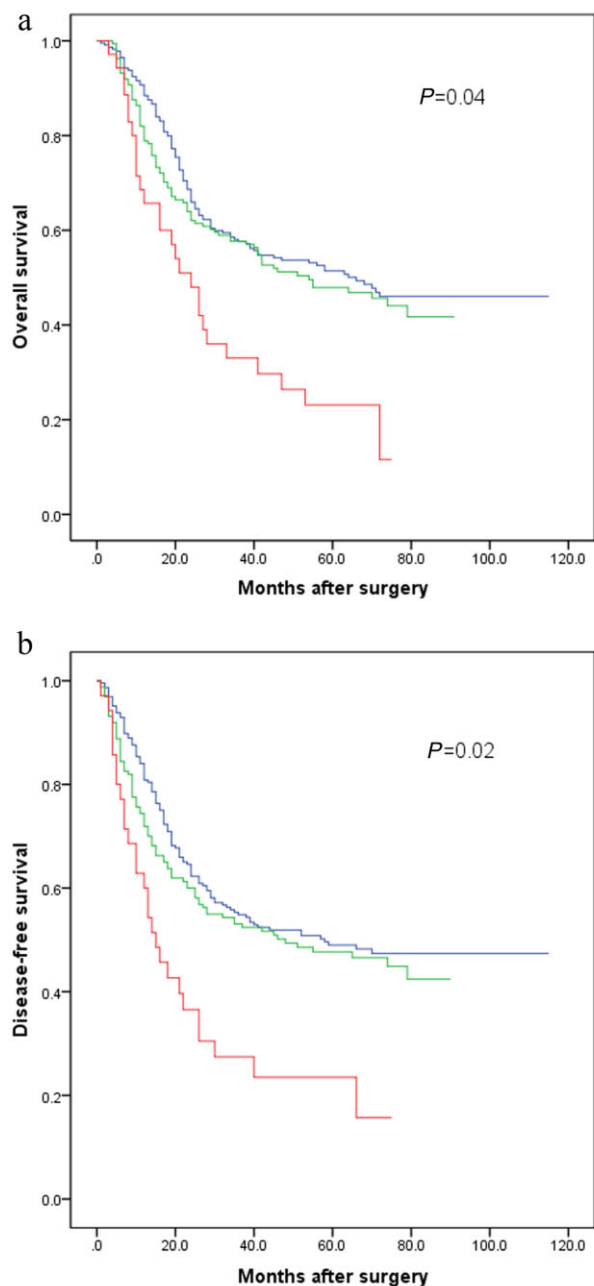


Figure 3 Comparison of overall survival according to a new combined prognostic model. The new combined model (including pN classification and BMI) could significantly stratify the risk (low, intermediate and high) for overall survival (a) and DFS (b) of ESCC patients. —, low-risk group; —, intermediate-risk group; —, high-risk group.

favourably associated with DFS and OS after controlling for clinicopathologic features.

Previous published studies have reported that patients with a higher BMI had a significantly better prognosis than those with a lower BMI.^{10,11,21} Our findings also indicated that

a high BMI is beneficial to ESCC patients. A clinical cohort study and meta-analysis both suggested that patients with higher a BMI had a favourable rate of survival when compared with those with a lower BMI. In our cohort study, overweight and obese patients had an apparently longer five-year OS than patients of normal weight. Multivariate survival analysis showed that BMI was an independent prognostic factor in esophageal cancer. However, some studies have produced conflicting results.^{18–20} These results may be attributed to: different pathological patterns; different BMI cut-off values in different studies; and patients who received neoadjuvant or adjuvant therapy were enrolled in some studies. In our study, patients were classified according to Asian-specific BMI cut-off values. In addition, patients who received neoadjuvant or adjuvant therapy were excluded. However, the underlying mechanisms were rarely elucidated and need to be further studied.

In the current study, 51.9% of ESCC patients had a high BMI and better OS and DFS compared with those with a normal/low BMI. Among patients with esophageal cancer, weight loss is common, caused by malnutrition because of reduced food intake (mostly related to dysphagia) and increased demands because of systemic inflammation (cancer cachexia).¹⁴ This may also be the reason for our results: BMI is one of the independent prognostic factors.

A recent study indicated that preoperative nutritional deficiency was associated with poor survival in cancer patients.²³ Overweight and obese patients might have a better nutritional status and potential survival advantage because they had large appetites and high lipid concentration, and could adequately preserve their fat and muscle mass.²⁴ We should acknowledge that the association between BMI and survival might be influenced by unmeasured confounding factors, such as selection criteria and, especially, socioeconomic status. Overweight and obese patients were thought to be associated with higher income and higher education conditions in China. They were more likely to receive chemotherapy and/or radiotherapy after recurrence than patients with a lower BMI because of financial support.

It has been suggested that the five-year OS of ESCC is 15–34%; therefore, suitable and individual management of ESCC is needed to improve the outcome for patients.^{2,3} TNM stage is traditionally considered the single most important prognostic factor of ESCC.⁶ Other features have been found to be factors for prognostic assessment of patients with ESCC. In this regard, tumor size, differentiation, location, performance status of the patient, tumor infiltration depth, lymph node status, and distant metastasis play a major role, and are extensively utilized in a clinical setting.^{25–28}

In the current study, we assessed a retrospective collection of ESCC patient data to determine the prognostic accuracy of

the pN classification alone compared to pN supplemented by BMI.

C-index analysis showed that the proposed new prognostic model (combined pN classification and BMI) could improve predictive ability when compared to the pN classification alone. Generally, our findings support the idea that the pN classification supplemented by BMI might improve the ability to discriminate ESCC patients' outcome. It is well known that pTNM stage and tumor differentiation are the best-established risk factors for important aspects affecting the prognosis of patients with ESCC.

Furthermore, the outcome for patients with the same stage following surgery is substantially different and such a large discrepancy has not been well understood. Our proposed prognostic model combining the pN classification with BMI might improve the ability to discriminate ESCC patient outcome. Thus, the BMI could be used as an additional effective instrument in identifying those ESCC patients at increased risk of tumor progression. To our knowledge, this is the first report to investigate the prognostic ability of the pN classification supplemented by BMI; however, further external validation of this important model is needed, using pooled multicenter data. This method might also help the clinician to choose a suitable therapy for the individual patient, for example, favoring a more aggressive treatment in patients with a high BMI.

Our study has a number of limitations: (i) it was a retrospective review; (ii) we included a relatively small number of patients; (iii) some of our findings are not consistent with the literature; and (iv) we did not include statistics of complications. However, the strengths of our study include: (i) that fact that it was a homogeneous study population (surgery only as therapy and no adjunctive therapy received); (ii) detailed analysis is provided; (iii) many of our findings are consistent with the literature; and (iv) we have proposed a new prognostic model for the treatment of ESCC.

Conclusion

In conclusion, our study showed that BMI could be considered a positive prognostic factor in ESCC patients. The new model we proposed can improve predictive ability in order to enhance patient survival. Finally, larger prospective studies in this area are warranted to confirm these preliminary results.

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Disclosure

No authors report any conflict of interest.

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