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Original Article

The Impact of Preoperative Low Body Mass Index on Postoperative Complications and Long-term Survival Outcomes in Gastric Cancer Patients

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: The aim of this study was to investigate the impact of preoperative low body mass index (BMI) on both the short- and long-term outcomes in patients with gastric cancer.
Materials and Methods: A total of 510 patients with gastric cancer were divided into the following 3 groups: low BMI group (≤18.5 kg/m^2, n=51), normal BMI group (18.6–24.9 kg/m^2, n=308), and high BMI group (≥25.0 kg/m^2, n=151).
Results: There were significantly more stage III/IV patients in the low BMI group than in the other groups (P=0.001). Severe postoperative complications were more frequent (P=0.010) and the survival was worse (P<0.001) in the low BMI group. The subgroup analysis indicated that survival was worse in the low BMI group of the stage I/II subgroup (P=0.008). The severe postoperative complication rate was higher in the low BMI group of the stage III/IV subgroup (P=0.001), although the recurrence rate and survival did not differ in the stage III/IV subgroup among all the BMI groups. Low BMI was an independent poor prognostic factor in the stage I/II subgroup (disease-free survival: hazard ratio [HR], 13.521; 95% confidence interval [CI], 1.186–154.197; P=0.036 and overall survival: HR, 5.130; 95% CI, 1.644–16.010; P=0.005), whereas low BMI was an independent risk factor for severe postoperative complications in the stage III/IV subgroup (HR, 17.158; 95% CI, 1.383–212.940; P=0.027).
Conclusions: Preoperative low BMI in patients with gastric cancer adversely affects survival among those with stage I/II disease and increases the severe postoperative complication rate among those with stage III/IV disease.

Keywords: Stomach neoplasms; Body mass index; Obesity; Underweight

INTRODUCTION

Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death [1]. In South Korea, gastric cancer is the second most prevalent cancer, and radical gastrectomy is the treatment of choice for this disease [2-5]. Although a patient's prognosis after a gastrectomy primarily depends on the disease stage [6,7], other factors such as body mass index (BMI), and nutritional and immunological status may also play an important role in the prognosis and have an impact on the short-term surgical outcomes [8-13].

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BMI can reportedly be a predictor of survival in patients with several cancers including colon, endometrial, ovarian, and pancreatic [14-18]. Some studies on gastric cancer have reported a negative impact of high BMI on short-term surgical outcomes, such as an increased operative time, blood loss, complications, and anastomotic leakage [19-22]. Chen et al. [23] recently reported that low and high BMI had poor prognostic impacts in gastric cancer patients with peritoneal dissemination and who underwent palliative chemotherapy. Lee et al. [24] reported a decreased overall mortality in patients with gastric cancer who had a high BMI at postoperative 1 year, but their baseline preoperative BMI had no prognostic impact. However, several recent studies have reported the negative impact of low BMI on the survival of patients with colorectal, lung, liver, and laryngeal cancers [25-30]. There have been only a few reports that assessed the impact of preoperative low BMI on the long-term survival outcomes of patients with gastric cancer. Therefore, we aimed to assess the impact of preoperative low BMI on the short-term surgical outcomes and long-term survival outcomes of patients with gastric cancer.

MATERIALS AND METHODS

We retrospectively collected data of 510 patients who were diagnosed with gastric cancer and who underwent a gastrectomy between January 2004 and May 2010 at the Department of Surgery, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea. This study was approved by the Institutional Review Board of the Catholic University of Korea (OC15RISI0067).

Clinicopathological evaluation

The evaluated parameters included patient demographics, comorbidity, operative details, and postoperative complications. The tumor depth, nodal status, and disease stage were classified according to the 7th American Joint Committee on Cancer staging system [31]. The lymph node dissection was classified according to the Guidelines of the Japanese Gastric Cancer Association [32].

Classification of BMI groups

The patients were classified into 3 groups according to their BMI, which was based on the International Obesity Task Force recommendation in Asian-Pacific populations [33]: group A, low BMI (≤18.5 kg/m^2, n=51); group B, normal BMI (18.6–24.9 kg/m^2, n=308); and group C, high BMI (≥25.0 kg/m^2, n=151). Each group was further subclassified into stage I/II and stage III/IV subgroups, and subgroup analysis was performed.

Blood sample analysis

Peripheral blood was acquired prior to surgery at the time of the diagnosis of gastric cancer. The serum albumin level, absolute lymphocyte count (ALC), and prognostic nutritional index (PNI) were used as the nutritional parameters. The ALC was calculated by multiplying the percentage of lymphocytes by the number of total white blood cells (WBCs). The PNI was calculated by the following formula:

$$10\times\text{serum albumin value (g/dL)}+0.005\times\text{ALC in peripheral blood}$$

The lymphocyte monocyte ratio (LMR) was defined as the ratio of the lymphocyte count to the monocyte count in the differential cell count.

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Short-term surgical outcomes and long-term survival outcomes

The short-term surgical outcomes were based on the perioperative surgical outcomes such as operation time, blood loss, extent of lymph node dissection, number of harvested lymph nodes, postoperative complications, and mortality rate. The postoperative complications were graded using the Clavien-Dindo classification [34], and severe postoperative complications included the complications classified as Clavien-Dindo grade IIIb or higher. Postoperative mortality was defined as death within 30 days after surgery or in-hospital death after surgery. To determine the long-term survival outcomes, the patients received follow-ups until their death, and the date of the last follow-up, recurrence-related information, disease-free survival (DFS), death-related information, and overall survival (OS) were obtained.

Statistical analyses

All variables are expressed as the mean±standard deviation. A 1-way analysis of variance was used to evaluate the continuous variables among the 3 groups and the χ^2 or Fisher's exact tests was used to evaluate the categorical variables. Multivariate logistic regression analyses were used to assess the factors associated with postoperative complications. The DFS and OS were calculated from the date of surgery. The survival adjusted for censoring was calculated using the Kaplan-Meier method, and the medians were compared using the log-rank test. The Cox proportional hazards model was used to assess the multivariate prognostic factor. A P value <0.05 was considered statistically significant.

RESULTS

Clinicopathologic characteristics

The clinicopathologic characteristics of patients in each group are shown in **Table 1**. Groups A, B, and C included 51 (10.0%), 308 (60.4%), and 151 (29.6%) patients, respectively. There were significantly more patients with stage III/IV gastric cancer (P=0.001) and with undifferentiated histology (P=0.011) in group A. The preoperative serum albumin level, ALC, PNI, and LMR were significantly lower in group A (P<0.001, P=0.027, P<0.001, and P<0.001, respectively). The postoperative complication rate was not significantly different among the groups, although the severe postoperative complication and mortality rates were significantly higher in group A (P=0.010 and P<0.001, respectively). Cancer recurrence was significantly more frequent in group A (P<0.001), although there were more patients with stage III/IV disease in group A (P=0.001). When the disease stage was subclassified into stage I/II and stage III/IV, the ALC and PNI were not found to differ in the stage I/II subgroup among the BMI groups, although there were more patients with low albumin levels and LMR in the stage I/II subgroup in group A (P=0.009 and P=0.004, respectively; **Table 2**).

The postoperative complication, severe postoperative complication, and mortality rates did not differ in the stage I/II group among the BMI groups, although cancer recurrence was significantly more frequent in group A (P=0.022). Nevertheless, in the stage III/IV subgroup of group A, the albumin level, PNI, and LMR were found to be significantly lower (P<0.001, P<0.001, and P=0.012, respectively). The severe postoperative complication and mortality rates were significantly higher (P=0.001 and P=0.002, respectively) in the stage III/IV subgroup of group A. The cancer recurrence rate was not significantly different in the stage III/IV subgroup among the BMI groups (P=0.400; **Table 2**).

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Table 1. Comparison of clinicopathologic characteristics of patients according to stratified BMI (n=510)

Characteristics	Group A (≤18.5)	Group B (18.6–24.9)	Group C (≥25)	P value
No. of patients	51	308	151	
Gender				0.121
Male	33 (64.7)	215 (69.8)	91 (60.3)	
Female	18 (35.3)	93 (30.2)	60 (39.7)	
BMI (kg/m^2)	17.5±1.1	22.0±1.7	27.0±1.6	<0.001
Age (years)	60.6±12.6	61.1±10.8	60.6±11.0	0.889
Comorbidity	25 (49.0)	167 (54.2)	61 (40.4)	0.021
Stage				0.001
Early (I, II)	20 (39.2)	194 (63)	112 (74.2)	
Advanced (III, IV)	31 (60.8)	124 (37)	39 (25.8)	
Operation type				0.004
Total gastrectomy	11 (21.6)	81 (26.3)	19 (12.6)	
Subtotal gastrectomy	40 (78.4)	227 (73.7)	132 (87.4)	
Approach				0.624
Open	22 (43.1)	144 (46.8)	76 (50.3)	
Laparoscopy	29 (56.9)	164 (53.2)	75 (49.7)	
Differentiation				0.011
Differentiated	17 (33.3)	156 (50.6)	87 (57.6)	
Undifferentiated	34 (66.7)	152 (49.4)	64 (42.4)	
Albumin (g/dL)	3.8±0.6	4.1±0.4	4.2±0.4	<0.001
ALC	1,734.1±718.7	2,004.9±722.0	2,152.2±1,399.4	0.027
PNI value	46.6±7.4	51.1±6.3	53.2±8.4	<0.001
LMR				<0.001
≥3.0	29 (56.9)	257 (83.4)	131 (86.8)	
<3.0	22 (43.1)	51 (16.6)	20 (13.2)	
Operation time (min)	251.5±118.1	286.5±560.1	246.8±67.7	0.624
Estimated blood loss (mL)	453.4±906.9	314.2±363.5	271.5±321.7	0.217
Lymph node dissection				<0.001
<D2	13 (25.5)	73 (23.7)	63 (41.7)	
≥D2	38 (74.5)	235 (76.3)	88 (58.3)	
Postoperative complication	9 (17.6)	44 (14.3)	26 (17.2)	0.119
Non-severe (C-D grade <IIIb)	3 (5.9)	33 (10.7)	17 (11.3)	
Severe (C-D grade ≥IIIb)	6 (11.8)	11 (3.6)	9 (6.0)	0.010
Postoperative mortality	5 (9.8)	2 (0.6)	4 (2.6)	<0.001
Recurrence*	16 (33.3)	75 (24.8)	16 (10.8)	<0.001

Values are presented as mean±standard deviation, and number (%).
BMI = body mass index; ALC = absolute lymphocyte count; PNI = prognostic nutritional index; LMR = lymphocyte to monocyte ratio; C-D = Clavien-Dindo classification.
*Three cases in group A, 6 cases in group B, and 3 cases in group C were excluded because the stage was IV.

Post-operative short-term outcomes

The univariate and multivariate analyses of the risk of severe postoperative complications, including mortality, in the stage I/II and stage III/IV subgroups indicated that low BMI (hazard ratio [HR], 17.158; 95% confidence interval [CI], 1.383–212.940; P=0.027) and PNI (HR, 6.440; 95% CI, 1.502–27.602; P=0.012) were the independent risk factors for severe postoperative complications in the stage III/IV subgroup (**Table 3**).

Post-operative long-term outcomes

The 5-year DFS was 61.2% in group A, 74.3% in group B, and 88.3% in group C; these values were significantly different (P<0.001). In the stage I/II subgroups, the 5-year DFS of group A was worse than that of the other groups (88.5%, 99.2%, and 98.6% in groups A, B, and C, respectively; P<0.001). However, the 5-year DFS did not differ in the stage III subgroups among the BMI groups (35.1%, 41.0%, and 47.4% in groups A, B, and C, respectively; P=0.431; **Fig. 1**).

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Table 2. Comparison of clinicopathologic characteristics of patients according to stratified BMI in gastric cancer patients with early stage (I, II; n=326) and advanced stage (III, IV; n=184) disease

Characteristics	Early stage (I, II)				Advanced stage (III, IV)			
	Group A (n=20)	Group B (n=194)	Group C (n=111)	P value	Group A (n=31)	Group B (n=114)	Group C (n=39)	P value
Gender				0.038				0.609
Male	9 (45.0)	133 (68.6)	31.4 (58.0)		24 (77.4)	82 (71.9)	26 (66.7)	
Female	11 (55.0)	61 (31.4)	47 (42.0)		7 (22.6)	32 (28.1)	13 (33.3)	
Age (yr)	60.2±13.9	61.9±10.5	60.3±10.7	0.428	60.84±11.9	59.7±11.2	61.4±11.7	0.696
Comorbidity				0.146				0.111
Yes	10 (50.0)	104 (53.6)	47 (42.0)		16 (51.6)	51 (44.7)	25 (64.1)	
No	10 (50.0)	90 (46.4)	65 (58.0)		15 (48.4)	63 (55.3)	14 (35.9)	
Stage				0.880				0.576
I/III	15 (75.0)	148 (76.3)	88 (78.6)		28 (90.3)	108 (94.7)	36 (92.3)	
II/IV	5 (25.0)	46 (23.7)	24 (21.4)		3 (9.7)	6 (5.3)	3 (7.7)	
Operation type				0.111				0.061
Total gastrectomy	3 (15.0)	32 (16.5)	9 (8.0)		8 (25.8)	49 (43.0)	10 (25.6)	
Subtotal gastrectomy	17 (85.0)	162 (83.5)	103 (92.0)		23 (74.2)	65 (57.0)	29 (74.4)	
Approach				0.656				0.300
Open	7 (35.0)	79 (40.7)	50 (44.6)		15 (48.4)	65 (57.0)	26 (66.7)	
Laparoscopy	13 (65.0)	115 (59.3)	62 (55.4)		16 (51.6)	49 (43.0)	13 (33.3)	
Differentiation				0.037				0.883
Differentiated	7 (35.0)	120 (61.9)	73 (65.2)		10 (32.3)	36 (31.6)	14 (35.9)	
Undifferentiated	13 (65.0)	74 (38.1)	39 (34.8)		21 (67.7)	78 (68.4)	25 (64.1)	
Albumin (g/dL)	4.1±0.4	4.2±4.2	4.3±0.3	0.009	3.6±0.5	4.0±0.4	4.0±0.4	<0.001
ALC	1,779.9±915.4	2,086.5±736.7	2,188.9±589.8	0.304	1,704.6±572.6	1,866.1±677.0	2,047.0±576.6	0.084
PNI value	51.7±1.2	52.2±0.4	54.1±9.1	0.075	44.3±6.9	49.4±5.9	50.6±5.0	<0.001
LMR				0.004				0.012
≥3	12 (60.0)	167 (86.1)	99 (88.4)		17 (54.8)	90 (78.9)	32 (82.1)	
< 3	8 (40.0)	27 (13.9)	13 (11.6)		14 (45.2)	24 (21.1)	7 (17.9)	
Operation time (min)	214.0±59.0	304.9±704.1	248.0±68.5	0.583	275.6±139.6	255.2±62.7	243.2±66.2	0.417
Estimated blood loss (mL)	302.1±399.6	281.0±352.6	229.0±245.0	0.353	551.1±1115.6	370.6±376.1	393.2±583.0	0.665
Lymph node dissection				0.057				0.043
<D2	11 (55.0)	111 (57.2)	79 (70.5)		8 (25.8)	12 (10.5)	9 (23.1)	
≥D2	9 (45.0)	83 (42.8)	33 (29.5)		23 (74.2)	102 (89.5)	30 (76.9)	
Postoperative complication	2 (10.0)	23 (54.8)	17 (15.2)	0.652	7 (22.6)	22 (19.3)	9 (23.1)	0.845
Non-severe (C-D grade <IIIb)	2 (100)	16 (69.6)	11 (64.7)	1.000	1 (14.3)	18 (81.8)	6 (66.7)	0.001
Severe (C-D grade ≥IIIb)	-	7 (30.4)	6 (35.3)		6 (85.7)	4 (18.2)	3 (33.3)	
Postoperative mortality	-	1 (0.5)	2 (1.8)	0.634	5 (16.1)	1 (0.9)	2 (5.1)	0.002
Recurrence	2 (10.0)	16 (8.2)	1 (0.9)	0.022	14 (50.0)	59 (54.6)	15 (41.7)	0.400

Values are presented as mean±standard deviation, and number (%).
ALC = absolute lymphocyte count; PNI = prognostic nutritional index; LMR = lymphocyte monocyte ratio; C-D = Clavien-Dindo classification.

The 5-year OS was 55.5% in group A, 72.4% in group B, and 81.0% in group C; these values were significantly different (P<0.001). In the stage I/II subgroups, the 5-year OS of group A was worse than that of the other groups (83.3%, 89.3%, and 95.7% in groups A, B, and C, respectively; P=0.008). However, the 5-year OS did not differ in the stage III/IV subgroups among the BMI groups (34.5%, 42.6%, and 38.5% in groups A, B, and C, respectively; P=0.797; **Fig. 2**). The Cox proportional hazards model for OS indicated that advanced stage (HR, 6.048; 95% CI, 3.969–9.216; P<0.001), undifferentiated histology (HR, 1.497; 95% CI, 1.018–2.201; P=0.040), and low LMR (HR, 1.666; 95% CI, 1.100–2.522; P=0.016) were independent poor prognostic factors in the overall patients. In the stage I/II subgroup, low BMI (HR, 5.130; 95% CI, 1.644–16.010; P=0.005) and low LMR (HR, 2.283; 95% CI, 1.046–4.979; P=0.038) were independent poor prognostic factors. In the stage III/IV subgroup, disease stage (HR, 2.298; 95% CI, 1.106–4.777; P=0.026) was the only independent poor prognostic factor (**Table 4**).

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Table 3. Risk factors for severe postoperative (Clavien-Dindo grade IIIb or higher) complications

Characteristics	Early stage (I, II)				Advanced stage (III, IV)			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Gender								
Female	1		1		1			
Male	0.305 (0.066–1.398)	0.126	0.276 (0.059–1.301)	0.104	1.139 (0.335–3.874)	0.835		
Age								
<61.2	1		1		1		1	
≥61.2	2.236 (0.674–7.411)	0.188	2.753 (0.811–9.344)	0.104	3.295 (0.876–12.390)	0.078	1.954 (0.405–9.436)	0.404
BMI*								
≥25					1		1	0.024
18.6–24.9					1.382 (0.150–12.750)	0.775	2.990 (0.254–35.183)	0.384
≤18.5					13.217 (1.551–112.607)	0.018	17.158 (1.383–212.940)	0.027
Comorbidity								
No	1				1		1	
Yes	0.830 (0.273–2.526)	0.743			2.386 (0.708–8.043)	0.161	3.339 (0.751–14.838)	0.113
Stage								
I/III	1		1		1		1	
II/IV	3.031 (0.986–9.315)	0.053	3.120 (0.995–9.783)	0.051	5.400 (1.261–23.121)	0.023	5.787 (0.899–37.257)	0.065
Differentiation								
Undifferentiated	1				1			
Differentiated	0.992 (0.317–3.102)	0.989			0.759 (0.237–2.426)	0.641		
Approach		0.741				0.776		
Open	1				1			
Laparoscopy	0.829 (0.272–2.523)				1.179 (0.380–3.655)			
Operation time								
<271.2	1				1			
≥271.2	0.630 (0.170–2.338)	0.490			2.074 (0.664–6.480)	0.209		
EBL								
<315.5	1		1		1			
≥315.5	1.084 (0.326–3.610)	1.084	0.849 (0.248–2.905)	0.795	0.994 (0.312–3.169)	0.992		
LND								
<D2	1				1			
≥D2	1.005 (0.321–3.144)	0.993			0.598 (0.154–2.320)	0.457		
Albumin								
≥4.1	1				1		1	
<4.1	2.019 (0.641–6.358)	0.230			4.835 (1.040–22.471)	0.044	3.843 (0.630–23.423)	0.144
ALC								
≥2,021.4	1				1			
<2,021.4	0.896 (0.295–2.727)	0.847			1.099 (0.344–3.505)	0.874		
PNI								
≥51.3	1				1		1	
<51.3	1.122 (0.358–3.511)	0.844			2.747 (0.814–9.264)	0.103	6.440 (1.502–27.602)	0.012
LMR								
≥3.0	1				1			
<3.0	1.787 (0.473–6.744)	0.392			2.047 (0.634–6.609)	0.231		

HR = hazard ratio; CI = confidence interval; BMI = body mass index; EBL = estimated blood loss; LND = lymph node dissection; ALC = absolute lymphocyte count; PNI = prognostic nutritional index; LMR = lymphocyte to monocyte ratio.
*There were no severe postoperative complications in all BMI groups with early stage disease (I, II).

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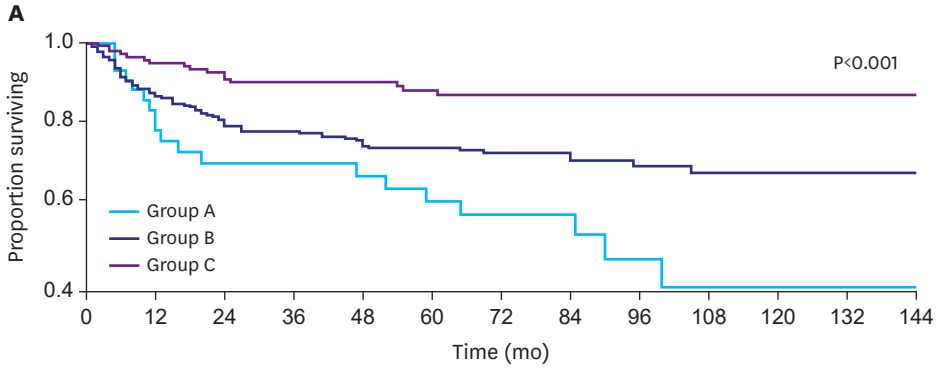
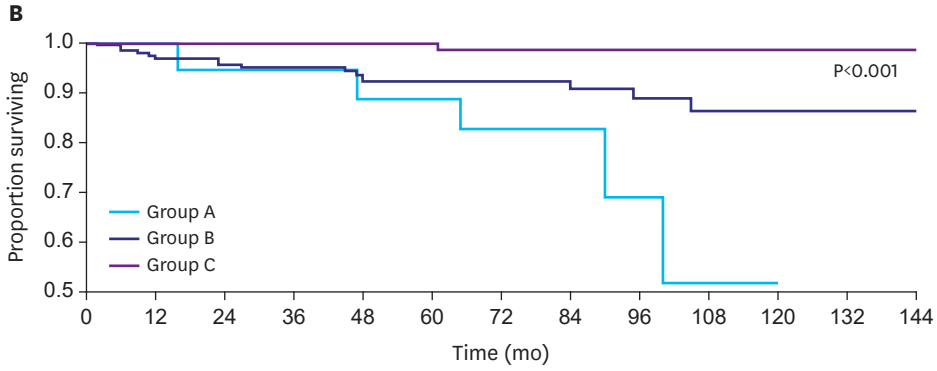
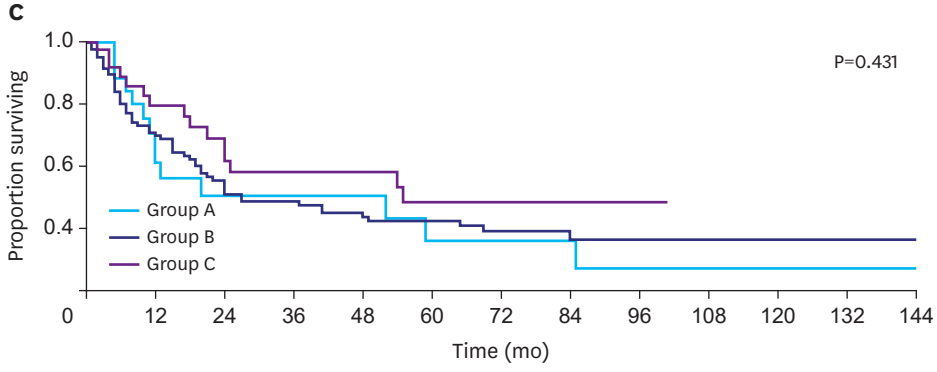


No. at risk													
Group A	51	34	25	24	22	20	14	12	8	5	3	1	1
Group B	308	240	208	188	171	134	111	79	51	39	22	11	3
Group C	151	127	119	107	97	82	69	42	27	18	15	6	1



No. at risk													
Group A	20	19	16	16	15	15	10	8	5	2	1	0	0
Group B	194	174	159	147	136	106	88	65	44	32	17	7	1
Group C	112	102	100	92	84	73	63	38	25	18	15	6	1



No. at risk													
Group A	31	15	9	8	7	5	4	4	3	3	2	1	1
Group B	114	66	49	41	35	28	23	14	7	7	5	4	2
Group C	39	25	19	15	13	9	6	4	2	0	0	0	0

Fig. 1. Kaplan-Meier DFS curves for gastric cancer patients, stratified by the BMI groups. (A) DFS in all patients, (B) DFS in stage I and II patients, and (C) DFS in stage III patients.
DFS = disease-free survival; BMI = body mass index.

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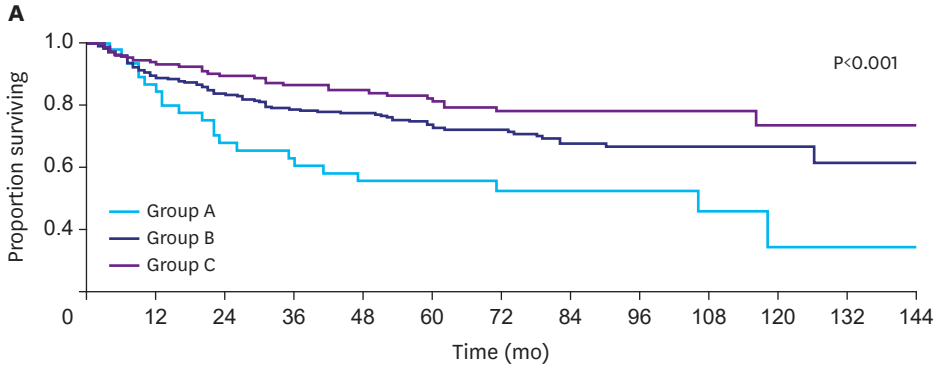
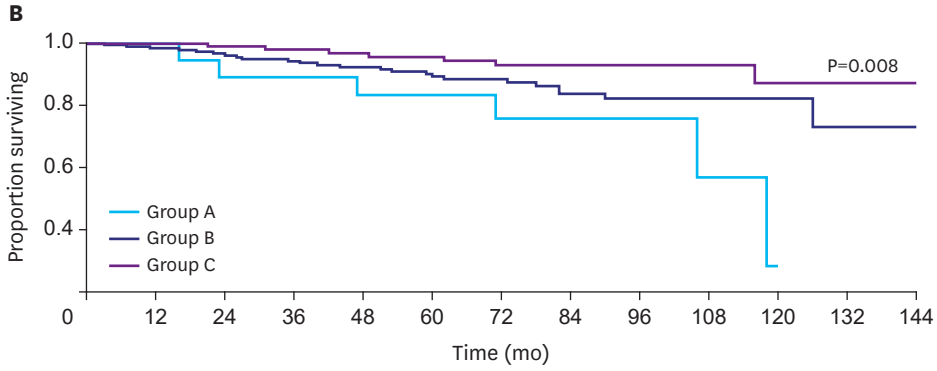
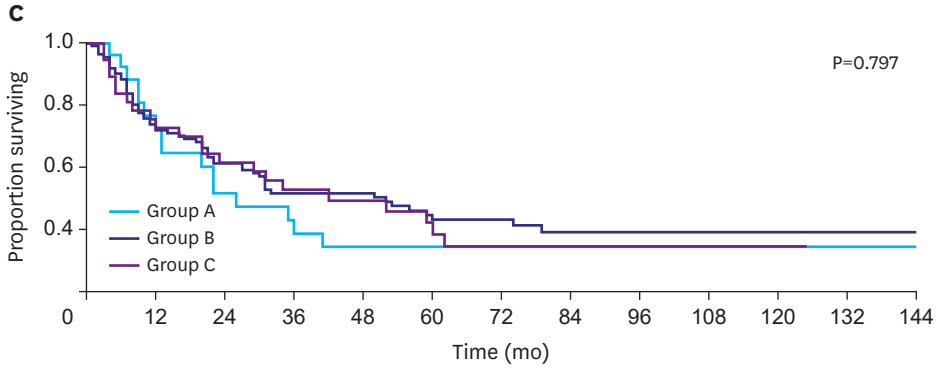


No. at risk													
Group A	51	38	28	26	22	22	14	12	9	7	3	1	1
Group B	308	259	227	199	178	139	116	81	55	40	22	11	3
Group C	151	129	122	110	99	86	71	43	28	19	16	6	1



No. at risk													
Group A	20	19	16	16	15	15	10	8	5	3	1	0	0
Group B	194	179	165	151	139	109	90	65	46	33	17	7	1
Group C	112	102	100	93	85	75	64	38	25	18	15	6	1



No. at risk													
Group A	31	19	12	10	7	7	4	4	4	4	2	1	1
Group B	114	80	62	48	39	30	26	16	9	7	5	4	2
Group C	39	27	22	17	14	11	7	5	3	1	1	0	0

Fig. 2. Kaplan-Meier OS curves for gastric cancer patients, stratified by the BMI groups. (A) OS in all patients, (B) OS in stage I and II patients, and (C) OS in stage III and IV patients.
OS = overall survival; BMI = body mass index.

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Table 4. Univariate and multivariate analyses of factors affecting overall survival according to the stratified stage

Characteristics	Sage I/II				Stage III/IV			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Gender								
Female	1		1		1			
Male	0.481 (0.227–1.023)	0.057	0.474 (0.216–1.038)	0.062	1.097 (0.710–1.697)	0.676		
Age								
<61.2	1		1		1		1	
≥61.2	1.540 (0.803–2.954)	0.194	1.217 (0.600–2.470)	0.586	1.412 (0.946–2.109)	0.091	1.083 (0.701–1.675)	0.719
BMI								
≥25	1	0.014	1	0.018	1	0.846		
18.6–24.9	2.200 (0.947–5.112)	0.067	1.911 (0.806–4.534)	0.142	0.941 (0.577–1.536)	0.807		
≤18.5	5.123 (1.715–15.308)	0.003	5.130 (1.644–16.010)	0.005	1.104 (0.580–2.104)	0.763		
Comorbidity								
No	1				1			
Yes	1.069 (0.560–2.043)	0.839			1.207 (0.811–1.798)	0.354		
Stage								
I/III	1		1		1		1	
II/IV	2.191 (1.123–4.272)	0.021	1.987 (0.915–3.931)	0.085	3.313 (1.711–6.415)	<0.001	2.298 (1.106–4.777)	0.026
Differentiation								
Differentiated	1				1		1	
Undifferentiated	1.449 (0.760–2.760)	0.260			1.357 (0.865–2.127)	0.184	1.534 (0.954–2.467)	0.077
Approach								
Open	1	0.210			1	0.299		
Laparoscopy	0.662 (0.347–1.263)				1.241 (0.826–1.864)			
Operation time								
<271.2	1				1		1	
≥271.2	0.914 (0.459–1.817)	0.797			1.405 (0.919–2.147)	0.116	1.522 (0.854–2.591)	0.085
EBL								
<315.5	1				1			
≥315.5	1.317 (0.660–2.628)	0.436			0.853 (0.563–1.291)	0.452		
LND								
<D2	1				1		1	
≥D2	0.992 (0.513–1.921)	0.982			0.570 (0.348–0.932)	0.025	0.724 (0.409–1.282)	0.268
Complication								
No	1		1		1			
Yes	2.272 (1.037–4.976)	0.040	1.971 (0.824–4.713)	0.127	1.219 (0.712–2.087)	0.469		
Albumin								
≥4.1	1		1		1		1	
<4.1	1.930 (0.981–3.799)	0.057	1.110 (0.448–2.751)	0.822	1.426 (0.953–2.134)	0.085	1.061 (0.639–1.762)	0.818
ALC								
<2,021.4	1				1			
≥2,021.4	1.080 (0.564–2.067)	0.817			0.808 (0.530–1.232)	0.322		
PNI								
≥51.3	1		1		1		1	
<51.3	1.932 (1.013–3.685)	0.046	1.275 (0.531–3.064)	0.587	1.677 (1.097–2.564)	0.017	1.468 (0.848–2.539)	0.170
LMR								
≥3.0	1		1		1		1	
<3.0	3.268 (1.640–6.513)	0.001	2.283 (1.046–4.979)	0.038	1.782 (1.152–2.757)	0.009	1.353 (0.827–2.214)	0.229

HR = hazard ratio; CI = confidence interval; BMI = body mass index; EBL = estimated blood loss; LND = lymph node dissection; ALC = absolute lymphocyte count; PNI = prognostic nutritional index; LMR = lymphocyte monocyte ratio.

DISCUSSION

We retrospectively investigated the impact of preoperative low BMI on the short-term surgical outcomes and long-term oncological outcomes of 510 patients with gastric cancer. The 5-year OS in the low BMI group was significantly worse compared to the normal and high BMI group. This finding appears to be natural, as the proportion of patients with stage III/IV in the low BMI

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group was significantly higher than that in the other BMI groups. However, when the patients were subclassified into stage I/II and stage III/IV subgroups, the 5-year OS in the low BMI group was significantly worse in only the stage I/II subgroup and not in the stage III/IV subgroup. In the Cox proportional hazards model for OS, low BMI was found to be an independent poor prognostic factor in only the stage I/II subgroup and not in the stage III/IV subgroup or the whole patient group. This indicates that the worse survival in the low BMI group among all the patients was primarily attributable to the worse survival in the stage I/II subgroup of the low BMI group. In fact, this is a unique finding in our study as compared to the findings of other recent studies that assessed the prognostic impact of low BMI in patients with gastric cancer [10,35,36]. Ejaz et al. [10] reported that the OS in low BMI patients was worse only when it was accompanied by low serum albumin levels. Wada et al. [35] reported that low BMI was an independent poor prognostic factor for OS and disease-specific survival. Migita et al. [36] reported that low BMI was an independent predictor of poor OS in only stage I disease, but it was associated with a higher rate of non-cancer-related death. In the present study, low BMI was associated with poor survival in only the stage I/II subgroup, and it was associated with a higher severe postoperative complication rate in only the stage III/IV subgroup. Unlike the results reported by Migita et al., the poor survival of the patients with low BMI and stage I/II disease in our study did not result from non-cancer-related death but mainly from cancer recurrence.

A low nutritional status among cancer patients is reportedly associated with a poor prognosis [37,38]. This observation appeared to be true in the stage I/II subgroup of our study, as there were significantly more patients with a low LMR in the low BMI group than in the high BMI group of the stage I/II subgroup. This finding may be linked to the depressive effect of protein-calorie malnutrition during cell-mediated antitumor immunity [39,40]. Low LMR and low BMI were independent poor prognostic factors of OS.

Previous studies suggested that LMR is a surrogate marker for the ratio of tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TMAs), which are important immune cells. TILs are thought to be responsible for cellular and humoral antitumor responses that contribute to tumor control. TMAs accelerate tumor progression through the production of growth factors and cytokines that subsequently lead to angiogenesis and anti-immune responses [13]. A recent study showed that LMR was an independent prognostic factor in gastric cancer patients, as in the present study [11]. However, low LMR was an independent poor prognostic factor in the stage I/II subgroup but not in the stage III/IV subgroup in the present study. Therefore, the poor prognostic impact of low BMI might disappear in the stage III/IV subgroup. Instead, low BMI was an independent risk factor for severe postoperative complications, including mortality, in the stage III/IV subgroup. The number of patients with a low LMR was not significantly different in the stage III/IV group compared to the other BMI groups. We postulate that the poor prognostic impact of low BMI is only applicable when the tumor burden is relatively small, as in the stage I/II subgroup in the present study. With an increase in the tumor burden, as in the stage III/IV subgroup of our study, the poor prognostic impact of low BMI cannot be applied. In contrast, the PNI in the stage III/IV subgroup of the low BMI group was significantly lower than in the stage III/IV subgroup of the normal and high BMI groups, unlike that noted in the stage I/II subgroup. Moreover, PNI was an independent prognostic factor for severe postoperative complications in the stage III/IV subgroup but not in the stage I/II subgroup. PNI serves as a factor that increases the surgical risk of patients, because the PNI was originally devised by Onodera et al. to assess the preoperative nutritional condition and to predict the surgical risk for patients with gastrointestinal malignancy [38].

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Our findings emphasize the importance of several immunological and nutritional indices including LMR and PNI, which can be easily calculated from routine laboratory examinations, in the perioperative management of patients with gastric cancer. If a patient with a low BMI has an LMR value <3 and a tumor of not more than stage II, including early gastric cancer, a more intensive follow-up program and adjuvant treatment plan, which are used in the treatment of advanced gastric cancer, are needed for the early detection and the prevention of recurrence. If a patient with a low BMI has a low PNI value and a tumor of more than stage II, more intensive nutritional support is needed during the pre-and postoperative management to prevent severe postoperative complications.

The present study has certain limitations. First, this was a relatively small-sized retrospective study, and the number of patients in the low BMI group was less than that in the normal and high BMI groups. Hence, there is a possibility of some selection bias. Second, the surgical mortality rate (9.8%) in the low BMI group was relatively higher than that in other gastrectomy series, although the surgical mortality rate of the entire patient group was 2.1% (11/510), which was not different from other gastrectomy series [41-43]. Third, we may have neglected the effect of obesity (BMI ≥30 kg/m^2) on the outcomes, because we considered this group to be a part of the high BMI group; there were only 8 obese patients (1.6%) in the present study, which is negligible. Nevertheless, more large-scale studies are needed to draw more conclusive results regarding the impact of low BMI on the outcomes of patients with gastric cancer. Finally, we did not investigate the difference between pre-operative and postoperative nutritional status and BMI, which may give an additional effect on the prognosis by poor nutrition-related repressed tumor-immunity.

In conclusion, preoperative low BMI in patients with gastric cancer adversely affects survival among those with stage I/II disease and increases the severe postoperative complication rate among those with stage III/IV disease. More consideration should be given to adjuvant treatment and follow-up programs in stage I/II disease for the prevention or early detection of recurrence and to preoperative preparation in stage III/IV disease to prevent severe postoperative complications when a gastric cancer patient with low BMI is treated.

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