Prognostic Value of Preoperative Body Mass Index for Diabetic Patients with Non-metastasis Gastric Cancer: A Single Center Experience

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Research article

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Abstract

AIM: This study was designed to investigate the prognostic effect of preoperative body mass index (BMI) for Type 2 diabetes mellitus (T2DM) patients with non-metastasis gastric cancer (GC) who underwent D₂ gastrectomy.

METHODS: T2DM patients with pT_{1-4b}N_{0-3b}M₀ GC were retrospectively collected in our cancer center from January, 2000 to December, 2010.

Chi-square test was used to analyze unordered categorical variables and ranked data, followed by Kaplan-Meier analysis as well as Cox regression models to detect risk factors for survival outcomes.

In addition, the cut-off point was determined by the X-tile program. All analyses were carried out using survival package of R and SPSS Software.

RESULTS: A total of 302 T2DM patients with pT_{1-4b}N_{0-3b}M₀ GC were collected and analyzed. The cut-off point of BMI, identified by the X-tile program, was 19 kg/m². Patients with low BMI (< 19 kg/m²) had a higher percentage of advanced T stage (T_{4a} and T_{4b}), more advanced TNM stage(stage IIIA, IIIB and IIIC), and more elevated level of serum carcinoembryonic antigen(CEA), compared to those with high BMI(>19 kg/m²)(all $P < 0.05$). In the low BMI subgroup, the 5-year overall survival rate was 39.02%, which was as high as 58.11% in the high BMI subgroup ($P < 0.05$). In the multivariate Cox regression model revealed that IIIC stage (OR= 3.101), N_{3b} stage (OR= 3.113) were the most important prognostic indicators, followed by pretreatment BMI (OR= 2.136).

CONCLUSION: Low preoperative BMI (<19 kg/m²) was a poor prognostic marker for T2DM patients with pT_{1-4b}N_{0-3b}M₀ GC.

Synopsis

Patients with low BMI (< 19 kg/m²) had a higher percentage of advanced T stage (T_{4a} and T_{4b}), more advanced TNM stage(stage IIIA, IIIB and IIIC), and more elevated level of serum CEA, lower 5-year overall survival rate compared to those with high BMI(>19 kg/m²). In the multivariate Cox regression model revealed that IIIC stage, N_{3b} stage were the most important prognostic indicators, followed by pretreatment BMI. So low preoperative BMI (<19 kg/m²) was a poor prognostic marker for T2DM patients with pT_{1-4b}N_{0-3b}M₀ GC.

Core Tip

Type 2 diabetes mellitus(T₂DM) has gradually become a growing global public health burden. The relationship between obesity and cancers has been well investigated and BMI is the most commonly used indicator. However, the current classification of BMI hardly matches the true circumstance. We enrolled 302 patients who had gastric cancers in this research and the cut-off point was set at 19 kg/m².

The low BMI(< 19 kg/m²) group showed a worse biological behavior and a lower 5-year overall survival rate. Moreover, our data showed that diabetic GC patients with low preoperative BMI(<19 kg/m²) were associated with a doubled mortality risk.

Introduction

Gastric cancer (GC) ranks the second in all cases of cancer-related mortality, accounting for approximately one million GC-related deaths per year^[1]. D₂ radical resection of the stomach combined with regional lymphadenectomy has been verified to be the single radical option^[2-6]. Although there has been great advance in diagnosis as well as treatment of GC, little progress has been achieved in long-term prognosis. Hence, it is particularly necessary to find a novel prognostic marker, which is noninvasive and accessible before treatment.

Type 2 diabetes mellitus (T₂DM) has gradually become a growing global public health burden [7]. the prevalence of T₂DM is up to 8.3% worldwide [8] according to the International Diabetes Federation, which varies in different regions and countries. It is estimated that 552 million people will develop diabetes by 2030 globally [8]. T₂DM may predispose patients to premature illness and death due to the relevant risks of cardiovascular diseases [9]. The prevalence of T₂DM has enhanced substantially in recent years, and the presence of T₂DM has been confirmed to be related with increased risks of multiple malignancies [10]. Moreover, and the relationship between diabetes mellitus (DM) and risks of developing cancers has been examined in numerous meta-analyses.

Obesity is an emerging risk factor for several cancers worldwide, and the relationship between obesity and cancers has been well investigated in various types of malignancies [11-14]. T₂DM is a multifactorial and chronic group of metabolic disorders characterized by hyperglycemia[7, 15], which is a result of obesity to some extent. In consideration of the relationship between obesity and long-term post-operative outcome in GC patients, several studies have revealed that obesity/overweight may correlate with the long-term outcome.

Body mass index (BMI) is the most commonly used index of body mass^[16]. Some authors have suggested a relationship between increased BMI and esophageal and gastric cardia adenocarcinoma^[17-19]. Conversely, some studies have demonstrated that high BMI was associated with a good prognosis of GC patients^[20, 21]. According to the World Health Organization (WHO) classification system, BMI is generally categorized into the following four grades^[22]: underweight (< 18.5kg/m²), normal weight (18.5kg/m²–24.9kg/m²), overweight (25.0kg/m²–29.9kg/m²), and obese ($\geq$ 30.0kg/m²). However, it hardly matches the true circumstance for the GC patients with T₂DM. The role of preoperative BMI on the survival of T₂DM patients with GC survival remains unclear. Hence, the retrospective study was designed to investigate the effect of preoperative BMI on the survival outcome in T₂DM patients with non-metastatic GC after D₂ gastrectomy.

Materials And Methods

Patients

From January 2000 to December 2012, a retrospective analysis was conducted of 302 non-metastasis consecutive diabetic patients with GC who underwent D₂ lymphadenectomy, at the department of gastrointestinal surgery, Fujian Cancer Hospital & Fujian Medical University Cancer Hospital. All of the patients were diagnosed with stage pT_{1-4b}N_{0-3b}M₀ GC according to the 7th edition of the TNM classification[23]. Data from these patients were entered into a prospectively maintained database.

The inclusion criteria were as follows: 1. non-metastasis GC; 2. adenocarcinoma conformed by histopathology; 3. physical fitness suitable for surgery; 4. D₂ lymphadenectomy; and 5. no prior history of any type of adjunctive therapy; 6. preprandial glucose > 7.1 mmol/L.

The exclusion criteria were as follows: 1. older than 80 years of age; 2. previous or concomitant other cancer; 3. previous or concomitant gastrectomy for benign disease; 4. previous chemotherapy or radiotherapy; 5. esophageal involvement; or 6. distant metastatic disease; 7. non-curative resection; 8. multiple primary malignancies; 9. remnant GC; 10. 15 retrieved lymph nodes, and 11. mortality within 30 days after surgery.

This data set included patient demographics (age and sex), pathologic characteristics (depth of invasion, number of metastatic lymph nodes, and number of examined lymph nodes), and follow-up data (follow-up duration and survival). The depth of invasion was categorized as mucosa, submucosa, proper muscle, subserosa, serosa, or adjacent organ invasion. The number of metastatic lymph nodes was categorized according to the node grouping of the seventh TNM classification[23]. Adjuvant chemotherapy was categorized as received or not received. Follow-up data were collected from hospital records for patients who were lost to follow-up. The follow-up duration was measured from the time of surgery to the last follow-up date, and information regarding the survival status at the last follow-up was collected.

All of the above patients were followed up by telephone interviews. The last follow-up was 1 January 2017. The logical and follow-up findings were collected and recorded in the database. All subjects gave written informed consent to the study protocol, which was approved by the Ethical Committees of Fujian Cancer Hospital & Fujian Medical University Cancer Hospital.

Surgery

According to the 7th edition NCCN guidelines[24], surgery with lymph node (LN) dissection is the primary treatment option for medically fit patients with resectable T_{1-4b}, any N tumors. All patients in the study underwent standard total or distal gastrectomy, depending on the location and macroscopic appearance of the primary tumor (Table 1). The strategy for LN dissections was determined using a standardized technique according to the guidelines of the 2010 Japanese Classification of Gastric Cancer and Gastric Cancer Treatment Guidelines edited by the Japanese Gastric Cancer Association[25].

Clinicopathological characteristics

The clinicopathological findings, including depth of tumor invasion and LN metastases, were utilized to stage tumors according to the 7th edition NCCN guidelines[24]. LNs were dissected and described according to the Japanese Classification of Gastric Carcinoma[25], which was also used to classify the location, histological type, and lymphatic invasion of tumors.

Statistical analysis

The associations between N category and clinic-pathological features were analyzed using Chi-square test. Risk factors for survival outcomes were identified by Kaplan-Meier analysis and Cox regression models. Only variables that were significance in univariate analysis were included in the multivariate model. The X-tile program(<http://www.tissuearray.org/rimmlab/>) which identified the cut-off with the minimum P values from log-rank χ^2 statistics was used to divide patients into high and low risk subsets, as previously described[26]. The primary endpoints of this study was cause specific survival (CSS). Deaths attributed to gastric cancer were treated as events, while other reasons caused deaths or survivors were defined as censored events. All analyses were performed with survival package of R(Version 3.2.1) and SPSS(Version 22.0). Prism 5 for Windows(Version 5.01, GraphPad Software) was used to draft the figure of Kaplan-Meier curve. Difference with P-value <0.05 was regarded as statistically significant.

Results

Identification of BMI cut-off points

X-tail plots, constructed in, illustrated that the optimal cut-off point of BMI was 19 kg/m² using minimum P value from log-rank $\div$ 2 test, with the strongest discriminatory capacity (**Fig.1**).

Clinicopathologic characteristics of patients

A total of 302 T₂DM patients with pT_{1-4b}N_{0-3b}M₀ GC, underwent D₂ radical resection, were collected for analysis. with 132 deaths in a median follow-up of 87.6 months (range 63 to 114 months). A detailed description of the associations between BMI level and clinic-pathological characteristics were presented in **Table 1**. As anticipated, patients with low BMI (<19 kg/m²) have high percentage of female, advanced T₄ category (T_{4a} and T_{4b}), advanced TNM category (stage III_A, III_B and III_C), and level of serum CEA (all P<0.05). In the low BMI subgroup, the percentage of T₄ category (79.3% vs 56.6%, P=0.002) and stage_{III} (79.3% vs 56.1%, P=0.002) was significantly higher in the low BMI subgroup than in the high BMI subgroup.

Survival analysis

The 5-year OS of T₂DM GC patients whose BMI less than 19 kg/m² and more than 19 kg/m² subgroups were 39.02% and 58.11%, respectively (**Fig.2**). At the same time, the risk level of BMI was built using the linear combination of BMI with the estimated regression coefficients derived from the above Cox

regression analysis as the weight to calculate the death risk score for each patient. Distribution of death and the survival status of stage I_A-III_C GC were shown in **Fig.3**. The plot of HRs for BMI sharply decreased as the level of BMI increased.

Independent prognostic factors in the training cohort

Variables considered significant in the multivariate analysis were entered in the Cox multivariate analysis. A total of 6 variables, including H.pylori infection (OR=1.439), Gender (OR=0.943) have no statistical power (all $P>0.05$). However, pretreatment BMI (OR=2.136), III_B category (OR=1.845), III_C category (OR=3.101), T_{4a} category (OR=1.617), T_{4b} category (OR=1.8), N_{1c} category (OR=1.701), N₂ category (OR=1.812), N_{3a} category (OR=2.145), and N_{3b} category (OR=3.113), respectively (all $P<0.05$) were proved independent in the multivariate Cox regression model (**Table 2, Fig.4**).

Discussion

To the best of our knowledge, our work is the first one to systematically assess the clinical significance of BMI level in T₂DM patients with non-metastatic GC. In spite of unclear underlying mechanisms, our study reveals that the pretreatment BMI is a significant indicator in predicting cancer-specific survival (CSS) in GC patients with T₂DM. In the Cox multivariate analysis, pretreatment BMI under 19 kg/m² was found to be an independent prognostic factor (OR = 2.136).

The important aspect in the intricate relation between the effect of BMI and GC is still unknown. Many investigation have been made on this relation, which harbor diverse results in terms of survival, pathological findings and surgical procedures[21, 27, 28]. Recent studies have reported a significantly decreased overall survival (OS) in underweight patients, defined as BMI under 18.5 kg/m², who previously underwent gastrectomy due to GC [29], indicating a close correlation between low BMI and poor prognosis in GC patients. Consistently, our study found that the pretreatment BMI is a significant predictor of CSS in GC patients with T₂DM. It was further confirmed that a preoperative BMI < 19 kg/m² was a predictor of poor prognosis.

Lymph node involvement has been verified as the most independently essential factor for survival of GC[30-34], whose accurate evaluation largely depends on the sufficiency of lymphadenectomy[35]. In our data, N_{3b} category (OR = 3.113) was the most vital indicator, followed by N_{3a} category (OR = 2.145), N₂ category (OR = 1.812), and N₁ category (OR = 1.701). Curative surgery of GC is rather tough in case of T₄ category, which includes tumor extension into serosa (T_{4a}) as well as surrounding organs and tissues (T_{4b}), which bears an unsatisfactory prognosis[36-38]. The 5-year survival rate of patients with T_{4a} GC has been reported to be rather low, 20% of whom pass away due to recurrence despite radical surgery of primary lesions. In the cohort, the percentage of T₄ was up to 79.3% in patients with BMI < 19 kg/m², and the corresponding data was 56.6% in the subgroup of BMI ≥ 19 kg/m² ($P = 0.002$). In the cox multivariate analysis, T_{4a} category (OR = 1.617), T_{4b} category (OR = 1.908) were found to be independent

risk factors. Pathologic TNM category is a helpful tool to predict prognosis in GC patients, nonetheless, a combination of preoperative BMI level can enhance predictive accuracy[39, 40]. In line with studies in other types of cancers, our findings demonstrated that low preoperative BMI (< 19 kg/m²) was a hazard factor for poor survival in patients with GC.

Our work was a retrospective single-institute study, which was the major limitation. Anyhow, our work demonstrated for the first time that pretreatment BMI was associated with the prognosis of GC patients with T₂DM. Specifically, a low pretreatment BMI predicted poor survival outcomes in GC patients with T₂DM. The application of BMI is efficient, cost-effective and easy-calculated compared to other invasive procedures.

Collectively, our data showed that low preoperative BMI(<19 kg/m²) was a prognostic factor for poor survival in patients with GC, and was useful in clinical practice and research design.

Declarations

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Authors' contributions

Zaisheng Ye and Shenghong Wei : Acquisition of data and drafting of the article; Zaisheng Ye, Qinying Liu and Qihong Zheng: participated in the data analysis; Yi Zeng, Yi Wang, Shu Chen and Zhitao Lin: Analysis and interpretation of the data and statistical expertise; Zaisheng Ye, Shenghong Wei and Luchuan Chen: Conception and design of the study. All of authors reviewed and approved the manuscript.

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Institutional review board statement:

This study was approved by Institutional Ethic Committee of Fujian Medical University Cancer Hospital.

Informed consent statement:

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by verbal consent. Individuals can't be identified according to the data presented.

Conflict-of-interest statement:

The authors declare no conflicts of interest regarding this manuscript.

Data sharing statement:

No additional data are available.

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Tables

Table 1. Demographics and clinicopathologic characteristics of patients with gastric cancer

	BMI < 19 kg/m2 (n=29)		BMI ≥ 19 kg/m2 (n=273)		P-value
H. Pylori infection					
Y	2	6.9%	17	7.2%	0.975
N	27	93.1%	220	92.8%	
Age	56.69±13.1		58.81±11.27		
	57(30-79)		59(23-82)		
Gender					
M	16	55.2%	180	75.9%	0.016
F	13	44.8%	57	24.1%	
CEA level	14.32±4.53		11.58±3.38		0.004
T category					
1a	-	-	22	9.3%	0.003
1b	-	-	22	9.3%	0.002#
2	3	10.3%	34	14.3%	
3	3	10.3%	25	10.5%	
4a	18	62.1%	127	53.6%*	
4b	5	17.2%	7	3%*	
N category					
0	4	13.8%	79	33.3%	0.301
1	7	24.1%	41	17.3%	0.082\$
2	7	24.1%	41	17.3%	
3a	6	20.7%	45	19%*	
3b	5	17.2%	31	13.1%*	
TNM category					
IA	0		34	14.3%	0.213
IB	1	3.4%	23	9.7%	0.002&
IIA	3	10.3%	20	8.4%	
IIB	2	6.9%	27	11.4%	
IIIA	6	20.7%	31	13.1%*	

IIIB	6	20.7%	37	15.6%*
IIIC	11	37.9%	65	27.4%*

Table 2 Cox Proportional Hazards Multivariate Regression Analysis Results

	B	SE	Wald	Sig.	Exp(B)	95.0% CI used for Exp(B)	
						Low	upper
H.pylori infection	.364	.368	.977	.323	1.439	.699	2.959
Gender	-.059	.254	.053	.818	.943	.573	1.552
BMI	.036	.005	43.388	.000	2.136	1.525	3.147
TNM category							
IA	1(reference)						
IB	-7.243	36.242	.040	.842	1.153	.514	2.584
IIA	-7.871	36.272	.047	.828	1.211	.704	2.130
IIB	-9.443	36.313	.068	.795	1.331	.654	2.411
IIIA	-10.091	36.359	.077	.781	1.411	.704	2.830
IIIB	-10.396	36.399	.082	.000	1.845	1.410	2.312
IIIC	-10.747	36.446	.087	.000	3.101	2.33	4.312
T category							
1a	1(reference)						
1b	5.579	17.095	.107	.744	1.153	.514	2.584
2	12.454	40.017	.097	.756	1.411	.704	2.830
3	14.452	40.041	.130	.718	1.230	.654	2.311
4a	14.850	40.063	.137	.012	1.617	1.308	3.130
4b	15.474	40.076	.149	.008	1.908	1.318	4.000
N category							
0	1(reference)						
1	2.678	1.090	6.036	.002	1.701	1.216	2.406
2	3.187	1.502	4.503	.000	1.812	1.322	2.517
3a	3.918	1.919	4.167	.000	2.145	1.510	3.034
3b	3.994	1.882	4.502	.000	3.113	2.133	4.539

Figures

Figure 1

X-tile analysis of survival data. X-tile analysis was done on gastric cancer patients with T2DM. The optimal cut-point highlighted in the left panels and a Kaplan-Meier plot (right panels). P values were determined by using the cut-point defined in the training set and applying it to the validation set. Figures show BMI count divided at the optimal cut-point (19 kg/m², $\chi^2=57.308$, $P<0.001$).

Hazard Ratio (logrank)	
Ratio (and its reciprocal)	2.196
95% CI of ratio	1.497 to 6.091

Figure 2

Survival analysis of gastric cancer patients with T2DM undergoing curative intent surgery. The P values for the survival comparison was determined by the log-rank test.

Figure 3

The risk score of BMI. The plot of HRs for BMI sharply increased as the number of BMI decreased.

Figure 4

Cox multivariate analyses of prognostic factors for the overall survival of non-metastatic gastric cancer patients with T2DM after D2 lymphadenectomy.