Prognostic value of preoperative body mass index for diabetic patients with non-metastasis gastric cancer: a single center experience

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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 pT1–4bN0–3bM0 GC were retrospectively collected in Department of Gastrointestinal Surgical Oncology, Fujian Cancer Hospital & Fujian Medical University Cancer Hospital from January, 2000 to December, 2010. These patients underwent D2 radical resection of the stomach combined with regional lymphadenectomy. 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 pT1–4bN0–3bM0 GC were collected and analyzed. The cut-off points 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 (T4a and T4b), 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), N3b 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 pT1–4bN0–3bM0 GC.

Keywords: BMI, Type 2 diabetes mellitus, Gastric cancer, X-tile, Survival rate
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, 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 (< 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥ 30.0 kg/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.

The inclusion criteria were as follows: (1) pathological diagnosis was adenocarcinoma; (2) D2 lymphadenectomy (according to the guidelines of the 2010 Japanese Classification of Gastric Cancer and Gastric Cancer Treatment Guidelines edited by the Japanese Gastric Cancer Association [24]; (3) I–III stage (AJCC TNM 7th edition) [25]; (4) preprandial glucose > 7.1 mmol/L.

The exclusion criteria were as follows: (1) > 80 years of age; (2) history of gastrectomy; (3) previous or combined with other cancer; (4) IV stage (AJCC TNM 7th edition; (5) history of neoadjuvant therapy; (6) non R0 resection; (7) mortality within non tumor causes [23].

The patients were conducted followed-up interviews over the telephone. The information regarding the survival status at the last follow-up was collected similar to the cohort of previous studies. The last follow-up was 1 January 2017 [23].

Statistical analysis
Chi-square test was used for qualitative data. The survival analysis was performed by the Kaplan–Meier and Cox regression methods. The X-tile program was used to determine the optimal cutoff [26]. 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. Values of $P$ < 0.05 were considered 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 ÷ 2 test, with the strongest discriminatory capacity (Fig. 1).

Clinicopathologic characteristics of patients
A total of 302 T2DM patients with $pT_1-4a, N_0-3p, M_0$ 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 IIIa, IIIb, and IIIc), and level of serum CEA (all $P$ < 0.05). In the low BMI subgroup, the percentage of $T_4$ category (79.3% vs 56.6%, $P$ = 0.002) and stage $\text{III}$ (79.3% vs 61.0%, $P$ = 0.001) 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–IIIC} GC were shown in Fig. 3. The plot of HRs for BMI sharply decreased as the level of BMI increased.

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                        | 17                        | 0.975   |
| N              | 27                       | 220                       |         |
| Age            | 56.69 ± 13.1             | 58.81 ± 11.27             |         |
|                | 57 (30–79)               | 59 (23–82)                |         |
| Sex            |                          |                           |         |
| M              | 16                       | 180                       | 0.016   |
| F              | 13                       | 57                        |         |
| CEA level      | 14.32 ± 4.53             | 11.58 ± 3.38              | 0.004   |
| T category     |                          |                           |         |
| 1a             | –                        | 22                        | 0.003   |
| 1b             | –                        | 22                        | 0.002   |
| 2              | 3                        | 34                        | 14.3%   |
| 3              | 3                        | 25                        | 10.5%   |
| 4a             | 18                       | 127                       | 53.6%   |
| 4b             | 5                        | 7                         | 3%      |
| N category     |                          |                           |         |
| 0              | 4                        | 79                        | 33.3%   |
| 1              | 1                        | 41                        | 17.3%   |
| 2              | 7                        | 41                        | 17.3%   |
| 3a             | 6                        | 45                        | 19%     |
| 3b             | 5                        | 31                        | 13.1%   |
| TNM category   |                          |                           |         |
| IA             | 0                        | 34                        | 14.3%   |
| IB             | 1                        | 23                        | 9.7%    |
| IIA            | 3                        | 20                        | 8.4%    |
| IIB            | 2                        | 27                        | 11.4%   |
| IIIA           | 6                        | 31                        | 13.1%   |
| IIIB           | 6                        | 37                        | 15.6%   |
| IIIC           | 11                       | 65                        | 27.4%   |

M: male; F: female; #: T4 VS T1-3; $: N3 VS N0-2; &: stage III VS stage I-II
Independent prognostic factors in the training cohort

Variables considered significant in the multivariate analysis were entered in the Cox multivariate analysis. A total of six variables, including *H. pylori* infection (OR = 1.439), sex (OR = 0.943) have no statistical power (all *P* > 0.05). However, pretreatment BMI (OR = 2.136), IIIb category (OR = 1.845), IIIc category (OR = 3.101), T4a category (OR = 1.617), T4b category (OR = 1.8), N1c category (OR = 1.701), N2 category (OR = 1.812), N3a category (OR = 2.145), and N3b 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,
N3b category (OR = 3.113) was the most vital indicator, followed by N3a 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 (T4a) as well as surrounding organs and tissues (T4b), which bears an unsatisfactory prognosis [36–38]. The 5-year survival rate of patients with T4a 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, T4a category (OR = 1.617), T4b 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. The phenomenon that obesity increase the risks of obesity-associated complications but decrease the mortality of patients which have critically illness is called “obesity paradox”. The underlying mechanism of obesity paradox still unclear but several explanations have been

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 | 0.364 | 0.368 | 0.977 | 0.323 | 1.439  | 0.699  | 2.959       |
| Sex              | −0.059 | 0.254 | 0.053 | 0.818 | 0.943  | 0.573  | 1.552       |
| BMI              | 0.036 | 0.005 | 43.388 | 0.000 | 2.136  | 1.525  | 3.147       |
| TNM category     |      |      |      |      |        |           |             |
| IA               |      |      |      |      |        |           |             |
| IB               | −7.243 | 36.242 | 0.040 | 0.842 | 1.153  | 0.514  | 2.584       |
| IIA              | −7.871 | 36.272 | 0.047 | 0.828 | 1.211  | 0.704  | 2.130       |
| IIIB             | −9.443 | 36.313 | 0.068 | 0.795 | 1.331  | 0.654  | 2.411       |
| IIIA             | −10.091 | 36.359 | 0.077 | 0.781 | 1.411  | 0.704  | 2.830       |
| IIIB             | −10.396 | 36.399 | 0.082 | 0.000 | 1.845  | 1.410  | 2.312       |
| IIIC             | −10.747 | 36.446 | 0.087 | 0.000 | 3.101  | 2.33   | 4.312       |
| T category       |      |      |      |      |        |           |             |
| 1a               |      |      |      |      |        |           |             |
| 1b               | 5.579 | 17.095 | 0.107 | 0.744 | 1.153  | 0.514  | 2.584       |
| 2                | 12.454 | 40.017 | 0.097 | 0.756 | 1.411  | 0.704  | 2.830       |
| 3                | 14.452 | 40.041 | 0.130 | 0.718 | 1.230  | 0.654  | 2.311       |
| 4a               | 14.850 | 40.063 | 0.137 | 0.012 | 1.617  | 1.308  | 3.130       |
| 4b               | 15.474 | 40.076 | 0.149 | 0.008 | 1.908  | 1.318  | 4.000       |
| N category       |      |      |      |      |        |           |             |
| 0                |      |      |      |      |        |           |             |
| 1                | 2.678 | 1.090 | 6.036 | 0.002 | 1.701  | 1.216  | 2.406       |
| 2                | 3.187 | 1.502 | 4.503 | 0.000 | 1.812  | 1.322  | 2.517       |
| 3a               | 3.918 | 1.919 | 4.167 | 0.000 | 2.145  | 1.510  | 3.034       |
| 3b               | 3.994 | 1.882 | 4.502 | 0.000 | 3.113  | 2.133  | 4.539       |

Fig. 4 Cox multivariate analyses of prognostic factors for the overall survival of non-metastatic gastric cancer patients with T2DM after D2 lymphadenectomy
proposed. Some researchers doubt the protective effect of obesity in patients because they think that selection bias of patients exists. Subjective viewpoint of observational study and meta-analysis and the validity of BMI in patient’s evaluation may also confound the results of study about obesity paradox [41]. On the other hand, some mechanism about how adipose tissue exert protective effect have been proposed. They claimed that adipose tissues may be a marker of better health status of patients and be a source of energy and lipid-soluble nutrients. Marques et al. reported that adipose tissues may modulate the immune system of patients which may help with the improved survival [42]. The result of our study is another evidence that higher BMI may help patients get better prognosis.

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.

**Conclusion**

Low preoperative BMI (<19 kg/m²) was a poor prognostic marker for T2DM patients with pT1–4aN0–3N0M0 GC.

**Abbreviations**

BMI: Body mass index; T2DM: Type 2 diabetes mellitus; GC: Gastric cancer; WHO: World Health Organization; TNM: Tumor–node–metastasis; NCCN: National Comprehensive Cancer Network.

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**Authors’ contributions**

ZY and SW: acquisition of data and drafting of the article; ZY, YX and QZ: participated in the data analysis; YZ, YW, SC and ZL: analysis and interpretation of the data and statistical expertise; ZY, SW and LC: conception and design of the study. All of authors reviewed the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

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

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare no conflicts of interest regarding this manuscript.

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