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Research Paper

Preoperative Metabolic Syndrome Is Predictive of Significant Gastric Cancer Mortality after Gastrectomy: The Fujian Prospective Investigation of Cancer (FIESTA) Study

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ABSTRACT

Metabolic syndrome (MetS) has been shown to be associated with an increased risk of gastric cancer. However, the impact of MetS on gastric cancer mortality remains largely unknown. Here, we prospectively examined the prediction of preoperative MetS for gastric cancer mortality by analyzing a subset of data from the ongoing Fujian prospective investigation of cancer (FIESTA) study. This study was conducted among 3012 patients with gastric cancer who received radical gastrectomy between 2000 and 2010. The latest follow-up was completed in 2015. Blood/tissue specimens, demographic and clinicopathologic characteristics were collected at baseline. During 15-year follow-up, 1331 of 3012 patients died of gastric cancer. The median survival time (MST) of patients with MetS was 31.3 months, which was significantly shorter than that of MetS-free patients (157.1 months). The co-existence of MetS before surgery was associated with a 2.3-fold increased risk for gastric cancer mortality ($P < 0.001$). The multivariate-adjusted hazard ratios (HRs) were increased with invasion depth T1/T2 (HR = 2.78, $P < 0.001$), regional lymph node metastasis N0 (HR = 2.65, $P < 0.001$), positive distant metastasis (HR = 2.53, $P < 0.001$), TNM stage I/II (HR = 3.00, $P < 0.001$), intestinal type (HR = 2.96, $P < 0.001$), negative tumor embolus (HR = 2.34, $P < 0.001$), and tumor size ≤4.5 cm (HR = 2.49, $P < 0.001$). Further survival tree analysis confirmed the top splitting role of TNM stage, followed by MetS or hyperglycemia with remarkable discrimination ability. In this large cohort study, preoperative MetS, especially hyperglycemia, was predictive of significant gastric cancer mortality in patients with radical gastrectomy, especially for early stage of gastric cancer.

1. Introduction

Gastric cancer is a malignant neoplasm with high mortality and is a major public health problem in the world (Van Cutsem et al., 2016). In China, gastric cancer is the second most common cancer and the second leading cause of cancer-related death largely due to late diagnosis and aggressive nature of the disease (Chen et al., 2016; Zhang et al., 2016; Fujita, 2009). Even with surgical management, the prognosis of gastric cancer is still unsatisfactory, with an estimated 5-year survival rate of 20–25% in China (Hartgrink et al., 2009). Considerable efforts have been made to determine the risk factors for gastric cancer and to identify biomarkers in order to enhance screening and early detection and to better predict the clinical outcomes (Saragoni et al., 2013; Tiberio et al., 2015; Oyama et al., 2013; Hiraki et al., 2011; Lv et al., 2015). In addition to intensified screening for early detection, it is of timely and clinical importance to find novel approaches to improve the prognosis and prolong the survival of patients with gastric cancer. One of the practical approaches is to determine easily obtainable clinical markers with prognostic significance to guide the optimal intervention and treatment strategies.

Metabolic syndrome (MetS) is composed of an array of metabolic diseases, including obesity, hyperglycemia, dyslipidemia, and high blood pressure, and has been known to be a major contributor to the increased cardiovascular disease and type 2 diabetes mellitus risk (Alberti

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et al., 2009). Recent studies also demonstrate a carcinogenic function of MetS in many types of cancer, including gastric cancer (Cantiello et al., 2015; Zhu et al., 2010; Pasanisi et al., 2006; Wei et al., 2014; Kim et al., 2014). Several large cohort studies from Western countries, including the United States, have investigated the association of MetS and single metabolic risk elements with gastric cancer development and clinical outcomes (Lin et al., 2015; Lindkvist et al., 2013). MetS, especially its component hyperglycemia, was identified as a promising risk factor for gastric cancer in women (Lin et al., 2015; Lindkvist et al., 2013). However, published data on the prognosis of preoperative MetS complication for gastric cancer mortality are very limited.

A retrospective study by Wei et al. revealed that preoperative MetS status was a significant and independent predictor for better survival among 587 Chinese patients with early stage gastric cancer (Wei et al., 2014). In contrast, another study among 505 Korean patients receiving radical gastrectomy for gastric cancer demonstrated that the coexistence of MetS before surgery increased the risk of gastric cancer mortality and control of MetS might improve the therapeutic efficacy (Kim et al., 2014). These conflicting and inconclusive results are likely due to the retrospective designs and a small cohort of patients in these studies (Wei et al., 2014; Kim et al., 2014). To better evaluate the potential contribution of preoperative MetS to the mortality of postoperative gastric cancer patients, we elicited a subset of data from the Fujian prospective investigation of cancer (FIESTA) study that incorporated 3012 patients with gastric cancer over a 15-year follow-up period.

2. Methods

2.1. The FIESTA Study

The FIESTA study initiated in January 2000 is an ongoing prospective cohort study of common digestive system tumors, including esophageal cancer, gastric cancer and colorectal cancer (Hu et al., 2016a; Peng et al., 2016; Hu et al., 2016b), and the purport of this study is to identify preoperative prognostic risk factors for cancer-specific mortality, which will help pinpoint underlying targets to delay tumor progression and prolong the survival of cancer patients after surgery. The conduct of this FIESTA study was approved by the Ethics Committee of Fujian Provincial Cancer Hospital and informed consent was obtained from all participants.

2.2. Study Population

Patients with gastric cancer who were eligible for radical gastrectomy were consecutively enrolled from the Department of Thoracic Surgery, Fujian Provincial Cancer Hospital between January 2000 and December 2010. The overall follow-up time ranged from 1.1 months to 183.3 months (median: 44.05 months). The last follow-up was completed in late 2015. Study patients with gastric cancer were recruited if they had no consanguinity and were Han Chinese without previous radical gastrectomy and without preoperative chemotherapy or radiotherapy. Total 3413 patients meeting these criteria were included in the current study.

2.3. Tissue Collection and Diagnosis

During the surgery, primary gastric cancer and adjacent normal tissue samples were collected from each patient, and the tissue samples were fixed in 10% neutral-buffered formalin for 20 h within 1 h after surgical removal and paraffin-embedded using standard procedures. The pathological analysis of tissue samples was completed at the Department of Pathology, Fujian Provincial Cancer Hospital. The diagnosis of gastric cancer was confirmed by preoperative biopsy or postoperative pathological examination.

2.4. Follow-up Assessment

The follow-up assessment for gastric cancer mortality was implemented every six to twelve months after discharge at the Out-Patient Department, Fujian Provincial Cancer Hospital or by phone calls or postal mails if the patients failed to appear and missed appointments. The clinical outcome of interest was cancer-specific mortality. The event was death from gastric cancer. Survival time was calculated by months. All patients were followed up from their initial admissions since January 2000 to their death or their last follow-up visit in 2015, whichever came first. Of the total 3413 patients recruited in this study, 118 patients were lost to follow-up, 48 patients had follow-up time <1 month, and 235 patients died of causes other than gastric cancer. Hence, 3012 patients with gastric cancer were assessed in final analysis. The follow-up time ranged from 1.1 months to 183.3 months at a median of 44.05 months. Over a 15-year period, 1331 patients died of gastric cancer and there were 1681 survivors. The minimum postoperative 5-year follow-up of all study patients enabled us to make predictions at the 5-year time point.

2.5. Metabolic Syndrome

The MetS is a cluster of metabolic abnormalities and there are several definitions (Grundy et al., 2004). In this study, we adopted the criteria proposed by the Chinese Diabetes Society (2004) (Association, 2004). MetS is define by at least three of the following criteria: (i) obesity: body mass index ≥ 25 kg/m^2; (ii) hyperglycemia: fasting blood glucose ≥ 6.1 mmol/L or 2-h plasma glucose ≥ 7.8 mmol/L or previously diagnosed diabetes; (iii) hypertension: systolic/diastolic blood pressure $\geq$ 140/90 mm Hg or under antihypertensive therapy; (iv) dyslipidemia: triglycerides ≥ 1.7 mmol/L or high-density lipoprotein cholesterol <0.9 mmol/L in men or <1.0 mmol/L in women.

2.5.1. Demographic and Clinicopathologic Characteristics

Patients were fasted overnight and fasting venous blood samples were collected to measure serum glucose, plasma triglycerides, total cholesterol, and high- and low-density lipoprotein cholesterol levels using standard procedures at the Clinical Laboratory, Fujian Provincial Cancer Hospital. Fasting blood glucose was determined by an automated glucose oxidase method.

In addition, patients were invited to finish a self-designed questionnaire to collect demographic information, including the date of birth, the age of onset for gastric cancer, gender, smoking and drinking status, and family history of cancer. Body weight and height were measured when patients were in light clothing and with bare feet. Blood pressure was measured with a conventional mercury sphygmomanometer on three occasions with at least 5 min intervals by certified examiners according to a standard protocol recommended by the American Heart Association (Perloff et al., 1993). Age was defined as the age at the time of surgery for gastric cancer. Body mass index was calculated as weight (in kilograms) divided by the square of height (in meters). Smoking status was classified as never smoking and ever smoking (including former and current smoking). Drinking status was classified as never drinking and ever drinking (including former and current drinking). A positive family cancer history referred to one or more of affected relatives within three generations who suffered malignancies except for non-melanoma skin cancer.

Clinicopathologic data were gleaned from the medical charts and pathological reports. These data include TNM stage (I, II, III and IV) (Edge and Compton, 2010), tumor size (in centimeters), depth of invasion (T1, T2, T3 and T4), regional lymph node metastasis (N0, N1, N2 and N3), distant metastasis (M0 and M1), Lauren's classification (intestinal type and diffuse type), and embolus (positivity and negativity).

2.6. Statistical Analysis

Continuous and categorical variables are expressed as mean (standard deviation) and count (percentage), respectively, and they were compared between the two groups by the *t*-test or Mann-Whitney *U* test or Chi-square test where appropriate. Survival time was estimated

by the Kaplan-Meier method and was compared by the Log-rank test. The measures of prognostic effect on gastric cancer mortality were expressed as hazard ratios (HR) and their 95% confidence intervals (CI) using the multivariate Cox or Weibull proportional hazards regression model before and after adjusting for confounding factors. Survival tree structure was generated by the STREE software (http://c2s2.yale.edu/software/stree/) (Zhang and Singer, 2010). To be specific, tree-structured survival analysis is based on a recursive partitioning algorithm and it can evaluate prognostic factors to determine the outcome. In a survival tree, the root node contains a sample of subjects from which the tree is grown-learning sample. All nodes in the same layer constitute a partition of the root node and an offspring node may use the same splitting factor as its ancestors. The recursive partitioning process proceeds until the tree is saturated in the sense that the offspring nodes subject to further division cannot be split. All statistical tests were two-sided, and $P < 0.05$ was accepted as statistical significance. Data were analyzed by the STATA software for Windows (StataCorp, TX, USA, version 13.0).

Table 1
The baseline characteristics of cohort patients by preoperative metabolic syndrome.

Characteristics	Patients without Mets ($N = 2501$)	Patients with MetS ($N = 511$)	P
Age	57.85 ± 11.31	61.76 ± 10.53	<0.001
Males	1868 (74.69%)	371 (72.60%)	0.325
BMI	22.21 ± 2.74	25.52 ± 3.04	<0.001
Ever smoking	472 (20.81%)	84 (16.44%)	0.026
Ever drinking	142 (6.26%)	26 (5.09%)	0.314
Family cancer history (+)	207 (9.13%)	51 (9.98%)	0.550
SBP (mm Hg)	120.90 ± 17.58	140.52 ± 19.45	<0.001
DBP (mm Hg)	75.42 ± 10.72	84.75 ± 11.44	<0.001
Fasting glucose (mmol/L)	5.73 ± 2.13	8.27 ± 2.74	<0.001
Triglyceride (mmol/L)	1.12 ± 0.79	1.61 ± 1.15	<0.001
TC (mmol/L)	4.50 ± 1.05	4.62 ± 1.17	0.022
HDLC (mmol/L)	1.09 ± 0.40	0.82 ± 0.27	<0.001
LDLC (mmol/L)	2.95 ± 0.91	3.10 ± 0.97	<0.001
Invasion depth			<0.001
T1	228 (9.76%)	26 (5.09%)	
T2	223 (9.55%)	32 (6.26%)	
T3	1280 (54.79%)	292 (57.14%)	
T4	605 (25.90%)	161 (31.51%)	
Regional LNM			<0.001
N0	672 (28.75%)	87 (17.03%)	
N1	733 (31.36%)	163 (31.90%)	
N2	738 (31.58%)	201 (39.33%)	
N3	194 (8.30%)	60 (11.74%)	
Distant metastasis			<0.001
Negative	2081 (89.12%)	415 (81.21%)	
Positive	254 (10.88%)	96 (18.79%)	
TNM stage			<0.001
I	305 (13.07%)	39 (7.66%)	
II	376 (16.11%)	48 (9.43%)	
III	1312 (56.21%)	304 (59.72%)	
IV	341 (14.61%)	118 (23.18%)	
Lauren's classification			0.048
Intestinal type	902 (39.77%)	178 (35.04%)	
Diffuse type	1366 (60.23%)	330 (64.96%)	
Tumor embolus			<0.001
Negative	1431 (63.07%)	263 (51.87%)	
Positive	838 (36.93%)	244 (48.13%)	
Tumor size (cm)	5.49 ± 2.97	6.10 ± 3.01	<0.001

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure, TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; LNM, lymph node metastasis; TNM, tumor node metastasis. Data are expressed as mean ± standard deviation or count (percentage). P was calculated by the *t*-test or Mann-Whitney *U* Test or Chisq test where appropriate.

3. Results

3.1. Baseline Characteristics

Patient baseline characteristics of the study cohort are summarized in Table 1. There were 2501 patients without MetS and 511 patients with MetS at baseline. The average age and BMI were significantly higher in patients with MetS than patients without ($P < 0.001$). The compositions for gender, ever smoking, ever drinking and positive family cancer history were comparable between patients with and without MetS. The average levels of systolic and diastolic blood pressure, fasting blood glucose, triglycerides and low-density lipoprotein cholesterol were significantly higher in patients with MetS than those without, while that of high-density lipoprotein cholesterol were significantly lower (all $P < 0.001$). Moreover, the clinicopathologic characteristics, including the distributions of invasion depth, regional lymph node metastasis, distant metastasis, TNM stage, Lauren's classification and tumor embolus, differed significantly between these two groups ($P < 0.001$). Tumor size was significantly larger in patients with MetS than those without ($P < 0.001$).

3.2. Association of MetS with Gastric Cancer Mortality

To explore the prognostic value of MetS in gastric cancer mortality, we examined the possible association between overall survival time and preoperative MetS status by the Kaplan-Meier method and Log-rank test (Fig. 1). The median survival time (MST) of patients with MetS was 31.3 months, which was significantly shorter than that of patients without MetS (157.1 months, $P < 0.001$) (Fig. 1: upper panel). As

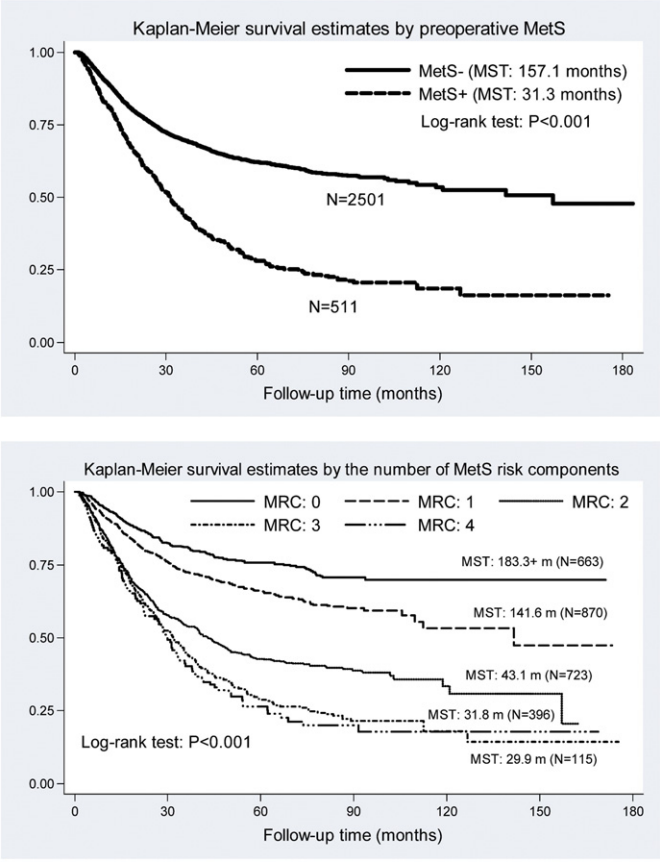


Fig. 1. Kaplan-Meier curves by metabolic syndrome (the upper panel) and the number of metabolic risk elements (the lower panel). Abbreviations: MetS, metabolic syndrome; MST, median survival time; MRC, metabolic risk component. The vertical axis represents the cumulative survival rate.

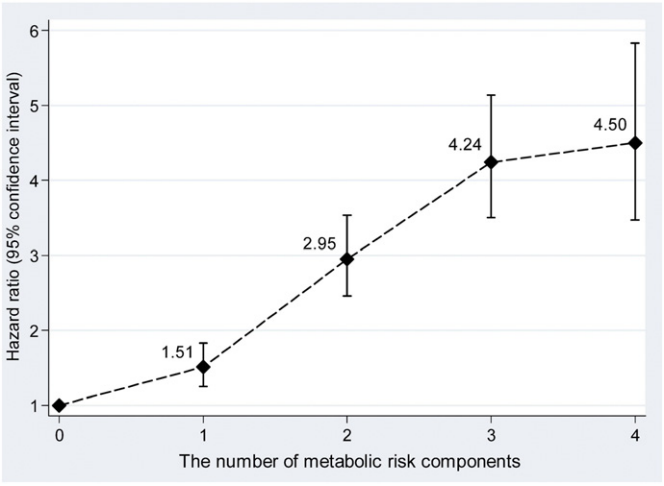


Fig. 2. The trend of effect-size estimates with the increasing number of metabolic risk components.

the ln(−ln(S(t))) is a linear function of ln(t) (here, t is time variable, and S(t) is survival function), it is proper to adopt the Weibull regression model for multivariate-adjusted survival analyses. The coexistence of MetS was associated with a 2.3-fold increased risk for gastric cancer mortality (HR = 2.30, 95% CI: 2.02–2.62, $P < 0.001$) after adjusting for age, gender, smoking, drinking, and family cancer history.

Survival differences were further explored based on the number of metabolic risk factors (from 0 to 4). The MST of patients declined with the increasing numbers of metabolic risk factors (183.3 + for 0, 141.6 for 1, 43.1 for 2, 31.8 for 3, and 29.9 months for 4) (Fig. 1, lower panel). The difference between patients with 0 and 1 risk factor was statistically significant ($P < 0.001$), while the difference between patients with 3 and 4 risk factors was not significant ($P = 0.441$) (Fig. 1: lower panel). In addition, gastric cancer mortality increased gradually in patients with increasing number of risk factors (HR = 1.51, 2.95, 4.24 and 4.50; 95% CI: 1.25–1.83, 2.46–3.53, 3.50–5.14 and 3.47–5.83, respectively, $p < 0.001$ for all groups) (Fig. 2). Altogether, these data suggest that preoperative MetS status is an independent risk factor and a potential predictor for the mortality of gastric cancer.

3.3. Association of MetS Components with Gastric Cancer Mortality

To further dissect the prognostic value of MetS, we evaluated the association of MetS components with gastric cancer mortality. These components include body mass index (BMI), systolic blood pressure (SBP), (diastolic blood pressure) DBP, fasting blood glucose, triglyceride, and high-density lipoprotein cholesterol (HDLC) (Table 2). Of these six MetS components, BMI was associated with a marginally increased risk for gastric cancer mortality (standard deviation (s.d.) increment: HR = 1.07, 95% CI: 1.01–1.13, $P = 0.029$) (Table 2), but the association became non-significant after adjusting for the confounding factors (e.g., age, gender, smoking and drinking status, and family history of cancer) (HR = 1.03, 95% CI: 0.97–1.09, $P = 0.358$) (Table 2). As for the rest 5 other components, gastric cancer mortality was moderately associated with the DBP (HR = 1.06, 95% CI: 1.00–1.13, $P = 0.044$) (Table 2). Mortality was significantly associated with SBP (HR = 1.11, 95% CI: 1.04–1.18, $P = 0.001$), fasting blood glucose (HR = 1.51, 95% CI: 1.44–1.57, $P < 0.001$), triglycerides (HR = 1.16, 95% CI: 1.11–1.22, $P < 0.001$), and high-density lipoprotein cholesterol (HR = 0.69, 95% CI: 0.64–0.74, $P < 0.001$) (Table 2). These data reveal a clear association between MetS components and gastric cancer mortality.

Table 3
Risk estimates of preoperative metabolic syndrome for gastric cancer mortality.

Group	HR, 95% CI, P	HR, 95% CI, P*
Overall	2.53, 2.24–2.85, <0.001	2.30, 2.02–2.62, <0.001
Invasion depth		
T1/T2	3.09, 1.74–5.46, <0.001	2.78, 1.50–5.14, <0.001
T3/T4	2.17, 1.92–2.45, <0.001	2.12, 1.86–2.43, <0.001
Lymph node metastasis		
N0	2.76, 1.84–2.36, <0.001	2.65, 1.73–4.07, <0.001
N1–N3	2.08, 1.83–2.36, <0.001	2.02, 1.76–2.32, <0.001
Metastasis		
Negative	2.66, 2.32–3.05, <0.001	2.53, 2.18–2.95, <0.001
Positive	0.93, 0.73–1.19, 0.562	0.88, 0.67–1.15, 0.340
TNM stage		
I/II	3.04, 1.99–4.64, <0.001	3.00, 1.91–4.70, <0.001
III/IV	2.04, 1.80–2.31, <0.001	1.99, 1.74–2.28, <0.001
Lauren's classification		
Intestinal type	3.02, 2.44–3.75, <0.001	2.96, 2.35–3.73, <0.001
Diffuse type	2.15, 1.86–2.49, <0.001	1.97, 1.68–2.32, <0.001
Tumor embolus		
Negative	2.48, 2.08–2.96, <0.001	2.34, 1.94–2.83, <0.001
Positive	2.14, 1.81–2.53, <0.001	2.05, 1.70–2.46, <0.001
Tumor size		
≤4.5 cm	2.62, 2.07–3.33, <0.001	2.49, 1.94–3.21, <0.001
>4.5 cm	2.17, 1.89–2.51, <0.001	2.09, 1.79–2.43, <0.001

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval. The effect-size estimates were calculated under the Weibull proportional hazards regression models. *P was adjusted for age, gender, smoking, drinking and family cancer history.

3.4. Stratified Analysis of MetS for Gastric Cancer Mortality

We next determined the effect-size estimates of MetS for gastric cancer mortality based on the clinicopathologic characteristics. The risk prediction of MetS was strikingly significant in all subgroups by clinicopathologic characteristics ($P < 0.001$) except for the subgroup with positive distant metastasis (Table 3). More importantly, the effect-size estimates increased with invasion depth T1/T2 (HR = 2.78, 95% CI: 1.50–5.14, $P < 0.001$), regional lymph node metastasis N0 (HR = 2.65, 95% CI: 1.73–4.07, $P < 0.001$), positive distant metastasis (HR = 2.53, 95% CI: 2.18–2.95, $P < 0.001$), TNM stage I/II (HR = 3.00, 95% CI: 1.91–4.70, $P < 0.001$), intestinal type (HR = 2.96, 95% CI: 2.35–3.73, $P < 0.001$), negative tumor embolus (HR = 2.34, 95% CI: 1.94–2.83, $P < 0.001$) and tumor size not exceeding 4.5 cm (HR = 2.49, 95% CI: 1.94–3.21, $P < 0.001$) after adjusting for age, gender, smoking and drinking status, and family history of cancer. Together, the stratified analysis suggests that MetS increases the risk of mortality in patients

Table 2
Risk estimates of preoperative individual metabolic factors for gastric cancer mortality.

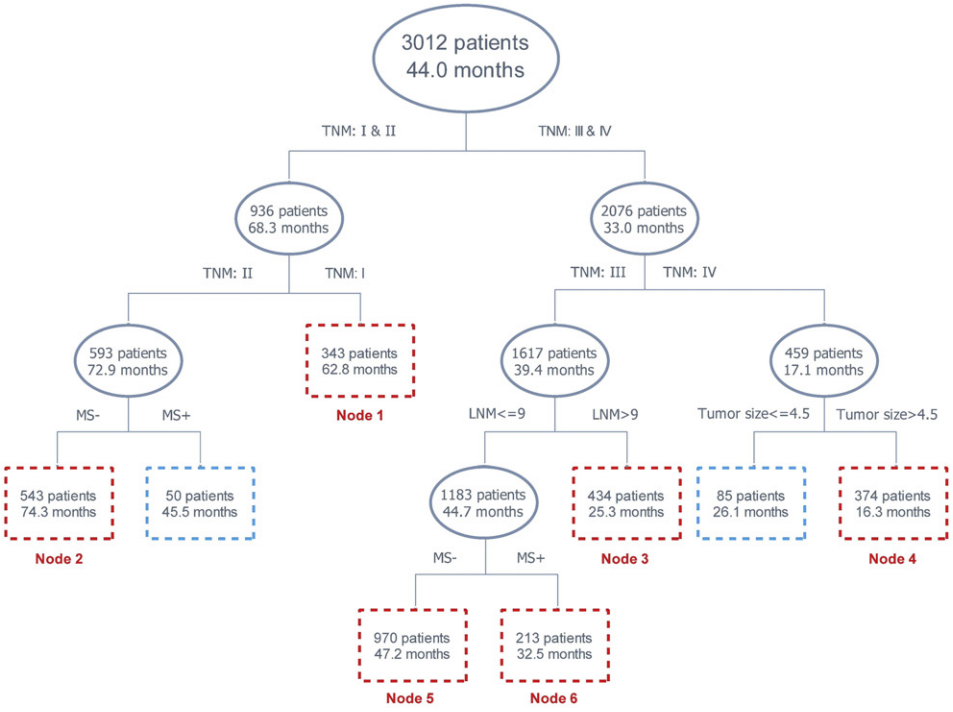
Metabolic factors	Increment (s.d.)	HR, 95% CI, P	HR, 95% CI, P*
BMI	3.07 kg/m^2	1.07, 1.01–1.13, 0.029	1.03, 0.97–1.09, 0.358
SBP	19.45 mm Hg	1.16, 1.10–1.23, <0.001	1.11, 1.04–1.18, 0.001
DBP	11.44 mm Hg	1.09, 1.04–1.16, 0.002	1.06, 1.00–1.13, 0.044
Fasting blood glucose	2.46 mmol/L	1.53, 1.47–1.60, <0.001	1.51, 1.44–1.57, <0.001
Triglyceride	0.88 mmol/L	1.15, 1.10–1.20, <0.001	1.16, 1.11–1.22, <0.001
HDLC	0.39 mmol/L	0.72, 0.67–0.77, <0.001	0.69, 0.64–0.74, <0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure, HDLC, high-density lipoprotein cholesterol; s.d., standard deviation; HR, hazard ratio; 95% CI, 95% confidence interval. The effect-size estimates were calculated under the Weibull proportional hazards regression models. *P was adjusted for age, gender, smoking, drinking and family cancer history.

with earlier stage of gastric cancer, especially in patients without distant metastasis. MetS also increases the risk of mortality in patients with intestinal type of gastric cancer compared to diffuse type of gastric cancer (Table 3).

3.5. Survival Tree Analysis of MetS for Gastric Cancer Mortality

To better evaluate the prognostic value of MetS, we performed tree-structured survival analysis of MetS along with the demographic and clinicopathologic characteristics for gastric cancer mortality (Fig. 3). For the MST of all the patients, the top splitting factor survival was TNM status. Patients with TNM stage I/II had significantly longer median follow-up time than patients with TNM stage III/IV (68.3 months vs. 33.0 months, $P < 0.001$) (Fig. 3). For patients with TNM stage II, MetS significantly shortened the median follow-up time (45.5 months with MetS vs. 74.3 months without MetS, $P < 0.001$). For patients with TNM stage III/IV, the secondary splitting factor was regional lymph node metastasis (cutoff value: 9) and tumor size (cutoff value: 4.5 cm), respectively (Fig. 3). MetS was only found to be strongly associated with declined median follow-up time in patients with TNM stage III and regional lymph node metastasis not exceeding 9 (32.5 months vs. 47.2 months, $P < 0.001$), but not in patients with TNM stage IV (Fig. 3). The discrimination ability of the tree-structured survival analysis was further confirmed by the Kaplan-Meier curves of



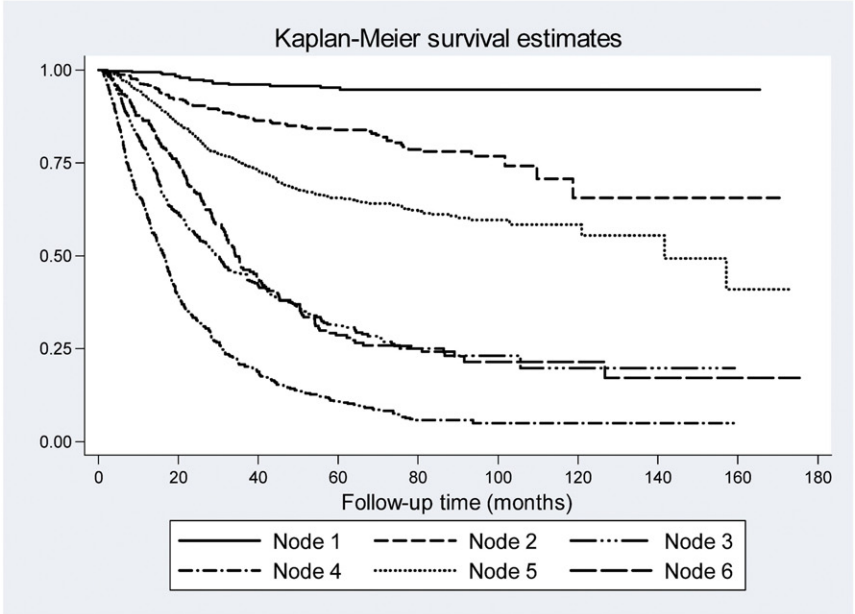


Fig. 3. Tree-structured survival analysis of MetS along with demographic and clinicopathologic characteristics (upper panel). Kaplan-Meier survival estimates of the generated nodes (lower panel) with sufficient power. Abbreviations: TNM, tumor node metastasis; MS, metabolic syndrome; LNM, lymph node metastasis. In the upper panel, the upper number in the box represents the number of patients and the lower number represents median follow-up time. In the lower panel, the vertical axis represents the cumulative survival rate.

the generated nodes with sufficient power (sample size >100) (Fig. 3, **lower panels**).

We further performed the tree-structured survival analysis of the MetS components along with the demographic and clinicopathologic characteristics for gastric cancer mortality (Fig. 4). For single metabolic risk elements, fasting blood glucose in both TNM stage I/II and III/IV split patients into two subgroups with distinct median follow-up time differences at a cutoff value of 6.11 and 6.17 mmol/L, respectively (Fig. 4). For patients with TNM stage I/II, the median follow-up time for patients with fasting blood glucose >6.11 mmol/L was shorter than that for patients with fasting blood glucose ≤6.11 mmol/L (55.4 months vs. 73.5 months, $P < 0.001$). For patients with TNM stage III/IV, the median follow-up time for patients with fasting blood glucose >6.17 mmol/L was roughly half of that for patients with fasting blood glucose, glycerame ≤6.17 mmol/L (22.8 months vs. 43.6 months, $P < 0.001$). These data suggest that elevated fasting blood glucose, hyperglycemia, is strongly associated with the mortality of gastric cancer patients, regardless of the TNM stage. The Kaplan-Meier curves of the generated

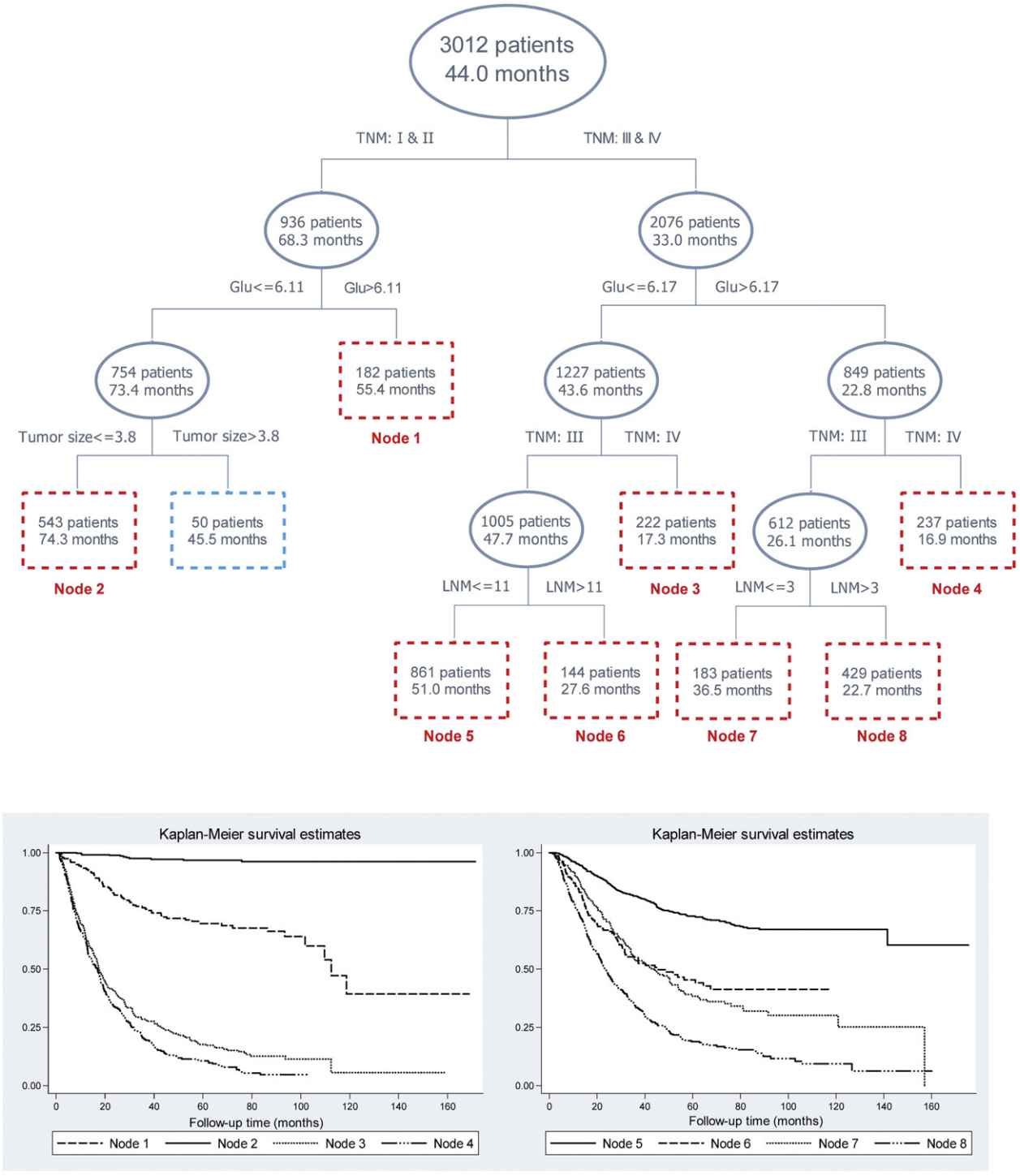


Fig. 4. Tree-structured survival analysis of metabolic risk elements along with demographic and clinicopathologic characteristics (upper panel). Kaplan-Meier survival estimates of the generated nodes (nodes 1–4, lower left panel; nodes 5–8, lower right panel) with sufficient power. Abbreviations: TNM, tumor node metastasis; LNM, lymph node metastasis; Glu, fasting blood glucose. In the upper panel, the upper number in the box represents the number of patients and the lower number represents median follow-up time. In the lower panels, the vertical axis represents the cumulative survival rate.

nodes with sufficient power (sample size >100) further confirmed the discrimination ability of the tree-structured survival analysis (Fig. 4, **lower panels**).

4. Discussion

On the basis of 3012 patients with gastric cancer from the FIESTA study, we analyzed the impact of the preoperative MetS status on the survival of patients after radical gastrectomy over a period of 15-year follow-up. We found that preoperative MetS, especially hyperglycemia, was predictive of significant gastric cancer mortality in patients with radical gastrectomy, especially for early stage of gastric cancer. To our knowledge, this is by far the largest cohort study to evaluate the association between the preoperative MetS and gastric cancer mortality.

The MetS is composed of a cluster of metabolic abnormalities, including obesity, hypertension, hyperglycemia, and dyslipidemia, with insulin resistance as the common pathophysiology (Samson and Garber, 2014). Mounting evidence suggests that insulin plays a pivotal role in the regulation of cell proliferation, differentiation, and apoptosis through insulin receptor and insulin-like growth factor 1 receptor, both of which are expressed in gastric cancer cells (Godsland, 2010; Salisbury and Tomblin, 2015; Bardou et al., 2013). The inhibition of these two receptors reduces cancer cell proliferation and accelerates cell death (Mu et al., 2012; Suda et al., 2014). As such, combating insulin resistance has been proposed as a useful preventive and therapeutic strategy for cancer therapy (Djiogue et al., 2013). It is likely that the strong association of preoperative MetS with poor survival of gastric cancer in our study results from the insulin resistance (Fig. 3). Additionally, we also found that the prognostic value of MetS was dominated by elevated fasting blood glucose (hyperglycemia) (Fig. 4). Glucose serves as an energy source for many cells, especially for the highly proliferative cancer cells, and has a direct tumor-promoting effect (Samani et al., 2007). Furthermore, hyperglycemia stimulates the generation of insulin and insulin-like growth factor 1 that in turn trigger tumor growth (Busaidy et al., 2015). Therefore, control of MetS, especially hyperglycemia, could improve the prognosis and prolong the survival of patients with gastric cancer.

Another important finding of this study is that the prognostic value of preoperative MetS for mortality was much better for patients in the early stage of gastric cancer than patients in the late stage (Fig. 3), highlighting the importance of closely monitoring MetS before and after radical gastrectomy. This result also suggests that proper interventions for MetS in low-risk patients would help reduce mortality and improve the survival of patients with gastric cancer.

Several limitations of our study need to be considered. First, we used BMI as an index of obesity. The other anthropometric indexes of obesity, such as waist circumference and hip circumference, are not available. This precludes the comparison of different components from the official MetS definition for their associations with gastric cancer mortality. In this study, we adopted the MetS definition that is more compatible with Chinese physical characteristics as proposed by the Chinese Diabetes Society in 2004 (Association, 2004). Second, the status of *Helicobacter pylori* infection, which plays an important role in the development of gastric cancer (Kim et al., 2014), is not available in current study. The residual confounding impact of *H. pylori* infection on the relationship between preoperative MetS and postoperative gastric cancer mortality cannot be completely ruled out. Third, all study patients were consecutively enrolled from the Fujian Provincial Cancer Hospital (single center) between January 2000 and December 2010. During this 10-year period, significant technical advances in gastrectomy might introduce a potential bias, compromising the impact of MetS or single metabolic risk element on gastric cancer mortality. Finally, the findings of this study cannot be directly extrapolated to all gastric cancer patients since only the postoperative gastric cancer patients were recruited in this study.

Taken together, our prospective findings demonstrate that preoperative MetS, especially hyperglycemia, was predictive of significant gastric cancer mortality in patients with radical gastrectomy. In addition, the prognostic value of preoperative MetS was much better for patients in the early stage of gastric cancer than patients in the late stage, calling for intensive surveillance of MetS in clinical practice. Pending its future validation in other large cohort studies, our findings could provide the basis for future personalized medicine, namely, gastric cancer patients with preoperative MetS should be identified early and treated with optimal regimens since these patients could have a poor survival probability.

Conflict of Interest

None declared.

Specific Author Contributions

FP, DH, XZ, WN planned and designed the study, and directed its implementation; FP, DH, XZ drafted the protocol; XL, GC, BL, HZ obtained statutory and ethics approvals; DH, XL, GC, KJ, HZ, BL contributed to data acquisition; FP, DH, XZ, WN had access to all raw data; DH, LC, WN did the data preparation, quality control and data analysis; FP, DH, WN, LC wrote the manuscript. All authors approved the final version of the submitted manuscript.

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