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Research Paper

Analysis of Preoperative Metabolic Risk Factors Affecting the Prognosis of Patients with Esophageal Squamous Cell Carcinoma: The Fujian Prospective Investigation of Cancer (FIESTA) Study

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ABSTRACT

Some metabolic factors have been shown to be associated with an increased risk of esophageal cancer; however the association with its prognosis is rarely reported. Here, we assessed the prediction of preoperative metabolic syndrome and its single components for esophageal cancer mortality by analyzing a subset of data from the ongoing Fujian prospective investigation of cancer (FIESTA) study. Between 2000 and 2010, patients who underwent three-field lymphadenectomy were eligible for inclusion. Blood/tissue specimens, demographic and clinicopathologic data were collected at baseline. Metabolic syndrome is defined by the criteria proposed by Chinese Diabetes Society. In this study, analysis was restricted to esophageal squamous cell carcinoma (ESCC) due to the limited number of other histological types. The median follow-up in 2396 ESCC patients (males/females: 1822/574) was 38.2 months (range, 0.5–180 months). The multivariate-adjusted hazard ratio (HR) of metabolic syndrome for ESCC mortality was statistically significant in males (HR, 95% confidence interval, P: 1.45, 1.14–1.83, 0.002), but not in females (1.46, 0.92–2.31, 0.107). For single metabolic components, the multivariate-adjusted HRs were significant for hyperglycemia (1.98, 1.68–2.33, <0.001) and dyslipidemia (1.41, 1.20–1.65, <0.001) in males and for hyperglycemia (1.76, 1.23–2.51, <0.001) in females, independent of clinicopathologic characteristics and obesity. In tree-structured survival analysis, the top splitting factor in both genders was tumor-node-metastasis stage, followed by regional lymph node metastasis. Taken together, our findings demonstrate that preoperative metabolic syndrome was a significant independent predictor of ESCC mortality in males, and this effect was largely mediated by glyeolipid metabolism disorder.

1. Introduction

Esophageal cancer is the fourth most common cancer in China, with a total of 477,900 new cases and 375,000 deaths projected to occur in 2015, and it is more common in males than in females (Chen et al., 2016). The two major histological types of esophageal cancer, viz. esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), which are distinct entities affected by diverse risk profiles, are now experiencing a global epidemiologic shift in recent decades (Brown and Devesa, 2002; Alexandre et al., 2014; Rustgi and El-Serag, 2014). Remarkably, compared with the most prevalent EAC in the U.S. and many Western countries, ESCC is the dominant histological type in China, and accounts for over 90% of esophageal cancer cases (Torre et al., 2015; Arnold et al., 2015). Despite recent substantial advances in clinical diagnostic and therapeutic tools (Sawayama et al., 2014; Messager et al., 2017), esophageal cancer exhibits an extremely poor prognosis with the 5-year survival rate of around 20% in China, mainly because it grows aggressively and is often diagnosed at an advanced stage (Zeng et al., 2015; Tseng et al., 2015; Klein and Stoecklein, 2009). One of the practical choices to improve overall survival is the identification of easy-to-obtain markers with prognostic

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significance for esophageal cancer by formulating more targeted and effective management strategies for high risk patients, such as metabolic profiling markers (Yakoub et al., 2010).

Large population-based studies have revealed that some metabolic factors such as obesity and diabetes are significant risk predictors for esophageal cancer, whereas the associated risk directions were not uniformly reported (Rustgi and El-Serag, 2014; Lindkvist et al., 2014; Lin et al., 2015; Alexandre et al., 2014). As for metabolic syndrome, several prospective studies have failed to identify its significant prediction for ESCC risk (Lin et al., 2015; Lindkvist et al., 2014). However, the prognostic prediction of metabolic risk factors has been reported only sparingly for esophageal cancer, except for a retrospective report by Wen et al. on the prognosis of preoperative metabolic syndrome among 596 patients with esophageal cancer (Wen et al., 2016). To our great surprise, they observed that the concomitance of metabolic syndrome before surgery was associated with better overall survival and tumor differentiation (Wen et al., 2016). This observation is somewhat counterintuitive based on what is known about the established relationship between metabolic syndrome and cancer risk (Esposito et al., 2012). Hence, a large prospective study is urgently needed to update our knowledge about the impact of metabolic syndrome on esophageal cancer prognosis. As an initial step toward meeting this need, we elicited a subset of data on esophageal cancer from the Fujian prospective investigation of cancer (FIESTA) study, and assessed the preoperative prediction of metabolic syndrome and its single components for esophageal cancer mortality.

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,b; Hu et al., 2017; Peng et al., 2016), 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.

2. Methods

2.1. Study Patients

In total, 2886 consecutive patients who underwent three-field lymphadenectomy for esophageal cancer and survived the hospitalization between January 2000 and December 2010 were enrolled from the Department of Thoracic Surgery, Fujian Provincial Cancer Hospital and followed up. The FIESTA study was approved by the Ethical Committee of the Fujian Provincial Cancer Hospital. Written informed consent was obtained from all patients and interview procedures and biospecimen collection were completed before surgery.

2.2. Eligibility Criteria

All study patients were hospitalized for the first time to receive surgery for esophageal cancer, which was clinically confirmed by preoperative biopsies or postoperative pathologic analyses. They had no history of any malignance except for the non-melanoma skin cancer and received no preoperative and postoperative chemotherapy or radiotherapy. Patients with recurrent esophageal cancer who had received treatment for the primary tumor elsewhere were excluded from the present study.

2.3. Tissue Collection

From each patient, paired cancer and normal esophagus tissues were resected, and they were fixed in 10% neutral-buffered formalin for 20 h within 1 h after surgical removal and paraffin-embedded using standard procedures. All tumor specimens were clinicopathologically analyzed at the Department of Pathology, Fujian Provincial Cancer Hospital.

2.4. Follow-up Assessment

After discharge from our hospital, follow-up was assessed every six to twelve months at the Out-Patient Department of 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 esophageal cancer. The time to event was calculated in months from the date of lymphadenectomy to the date of death or the date of the last follow-up, whichever came first. The minimum postoperative 5-year follow-up of all study patients enabled us to make predictions at the 5-year time point.

2.5. Definition of Metabolic Syndrome

Metabolic syndrome is a cluster of metabolic abnormalities, and there are currently several official definitions (Grundy et al., 2004). In this study, we adopted the diagnostic criteria proposed by the Chinese Diabetes Society in 2004 (Association, 2004), that is, metabolic syndrome is defined by the presence of three or more of the following criteria: (i) obesity: body mass index ≥ 25 kg/m^2; (ii) hyperglycemia: fasting blood glucose ≥ 6.1 mmol/L or 2-hour plasma glucose ≥ 7.8 mmol/L or previously diagnosed diabetes; (iii) hypertension: systolic/diastolic blood pressure ≥ 140/90 mmHg or under antihypertensive therapy; (iv) dyslipidemia: triglycerides ≥ 1.7 mmol/L or high-density lipoprotein cholesterol <0.9 mmol/L in males or <1.0 mmol/L in females.

2.6. Demographic and Clinicopathologic Characteristics

The day before surgery, patients were fasted overnight and fasting venous blood samples were drawn for measuring serum fasting blood glucose, plasma triglycerides, total cholesterol, high-density and low-density lipoprotein cholesterol. Fasting blood glucose was determined by an automated glucose oxidase method. All measurements were uniformly completed according to standard procedures at the Clinical Laboratory, Fujian Provincial Cancer Hospital.

At enrollment, patients were invited to finish a self-designed questionnaire covering demographic and anthropometric characteristics, including date of birth, age at surgery for esophageal cancer, gender, smoking, drinking and family cancer history. Body weight and height were measured when patients were in light clothing and with bare feet, and body mass index was calculated as weight (in kilograms) divided by the square of height (in metres). Blood pressure was measured with a conventional mercury sphygmomanometer on three occasions of at least 5 min intervals by certified examiners according to the standard protocol recommended by the American Heart Association (Perloff et al., 1993). Smoking status was categorized as ever (former/current) versus never. Drinking status was categorized as ever (former/current) versus never. The family cancer history was recorded to be positive if one or more of affected relatives within three generations had suffered any malignance except for non-melanoma skin cancer.

After surgery, clinicopathologic data were extracted from pathological reports, including histological type of esophageal cancer (ESCC, EAC and esophageal neuroendocrine carcinomas), tumor size (in centimeters), tumor node metastasis (TNM) stage (I, II, III and IV according to the 7th Edition of the UICC/AJCC TNM Staging System (Edge and Compton, 2010)), depth of invasion (T1, T2, T3 and T4), regional lymph node metastasis (LNM) (N0, N1, N2 and N3), distant metastasis (M0 and M1), tumor location (upper, middle and lower esophagus), histological differentiation (well, moderate and poor differentiation) and tumor embolus (positivity).

2.7. Statistical Analyses

Continuous data are expressed as mean ± standard deviation and categorical data as number (percentage). Two-group comparisons

were quantified by the unpaired *t*-test or the Mann-Whitney *U* test or the χ^2 test, where appropriate. Kaplan-Meier curves along with Log-rank tests were used to depict and test the differences of cumulative survival rates. Adjusted risk estimates (hazard ratio or HR and its 95% confidence interval or 95% CI) for mortality were calculated using the multivariate Weibull proportional hazards regression analysis. Survival tree structure was built by the STREE software (available at the website: 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 a probability of less than 0.05 was considered to be statistically significant. All statistical analyses and graphics were completed with the STATA software for Windows (StataCorp, TX, USA, version 13.0) unless otherwise indicated.

3. Results

3.1. Follow-up Observation

As of December 2015, 147 patients were lost to follow-up and 204 patients died of causes other than esophageal cancer (Here, their baseline and clinicopathologic characteristics can be seen in Supplementary Table S1), leaving 2535 assessable patients aged 30–88 years for survival analysis. The 5-year survival rate was 52.2%, which was comparable with that of previous reports (Kang et al., 2007; Nishimaki et al., 1999). Over a 15-year follow-up period, there were 1265 deaths from esophageal cancer and 1270 survivors left. Based on the histological types, there were 2396 patients with ESCC, 83 patients with EAC and 56 patients with esophageal neuroendocrine carcinomas. In view of statistical power, the following analyses were only restricted to ESCC patients, including 1822 males and 574 females. The median follow-up period in all ESCC patients was 38.2 months (range, 0.5–180 months).

3.2. Patient Characteristics

The baseline and clinicopathologic characteristics of cohort patients with ESCC are summarized in Table 1. Male patients tended to be younger and have lower body mass index than female patients (both $P < 0.001$). The percentages of ever smokers and ever drinkers were extremely higher in males than in females (both $P < 0.001$), so was the positive family cancer history ($P = 0.026$). Mean values of systolic and diastolic blood pressure, as well as mean concentrations of fasting blood glucose and triglycerides were comparable between genders, whereas mean concentrations of total cholesterol, high-density and low-density lipoprotein cholesterol were significantly lower in males than in females (all $P < 0.001$). The percentage of metabolic syndrome was 10.48% in males and 12.20% in females ($P = 0.251$). For clinicopathologic characteristics, the distributions of esophageal location, histological differentiation and tumor embolus between genders were comparable. In contrast, there was a higher percentage of deep invasion (T3–T4) or advanced TNM stage (III) in males than in females, yet a lower percentage of negative regional LNM (N0) (all $P < 0.001$). The tumor size was significantly larger in males than in females ($P < 0.001$).

Table 1
The baseline and clinicopathologic characteristics of cohort patients with esophageal squamous cell carcinoma.

Characteristics	Males (n = 1822)	Females (n = 574)	P
Age at surgery (years)	55.98 ± 9.81	57.93 ± 9.41	<0.001
Body mass index (kg/m^2)	22.14 ± 2.90	22.83 ± 3.26	<0.001
Ever smoking	986 (54.12%)	16 (2.79%)	<0.001
Ever drinking	473 (25.96%)	8 (1.39%)	<0.001
Family cancer history (+)	268 (14.71%)	63 (10.98%)	0.026
Systolic blood pressure (mmHg)	123.74 ± 18.22	125.33 ± 18.28	0.070
Diastolic blood pressure (mmHg)	77.34 ± 10.43	78.24 ± 10.73	0.073
Fasting blood glucose (mmol/L)	6.04 ± 2.52	6.22 ± 2.53	0.142
Triglycerides (mmol/L)	1.19 ± 0.90	1.18 ± 0.83	0.714
Total cholesterol (mmol/L)	4.78 ± 1.04	5.06 ± 1.02	<0.001
HDL cholesterol (mmol/L)	1.10 ± 0.42	1.23 ± 0.42	<0.001
LDL cholesterol (mmol/L)	3.15 ± 0.95	3.31 ± 0.92	<0.001
Metabolic syndrome	191 (10.48%)	70 (12.20%)	0.251
Esophagus location			0.205
Upper	179 (9.82%)	60 (10.45%)	
Middle	1453 (79.75%)	469 (81.71%)	
Lower	190 (10.43%)	44 (7.67%)	
Histological differentiation			0.838
Well	278 (15.26%)	84 (14.63%)	
Moderate	1216 (66.74%)	381 (66.38%)	
Poor	328 (18.00%)	109 (18.99%)	
Depth of invasion			<0.001
T1–T2	447 (24.53%)	233 (40.59%)	
T3–T4	1375 (75.47%)	341 (59.41%)	
Regional LNM			<0.001
N0	710 (38.97%)	286 (49.83%)	
N1	522 (28.65%)	161 (28.05%)	
N2	383 (21.02%)	92 (16.03%)	
N3	207 (11.36%)	35 (6.10%)	
Tumor embolus (+)	312 (17.12%)	81 (14.11%)	0.089
TNM stage			<0.001
I	140 (7.68%)	83 (14.46%)	
II	560 (30.74%)	221 (38.50%)	
III	1123 (61.64%)	270 (47.04%)	
Tumor size (cm)	4.66 ± 2.06	4.02 ± 1.86	<0.001

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; LNM, lymph node metastasis; TNM, tumor node metastasis. Data are expressed as mean ± standard deviation or number (percentage). P was calculated by the *t*-test or the Mann-Whitney *U* test or the Chisq test where appropriate.

3.3. Overall Analyses

As shown in Fig. 1, Kaplan-Meier curves were generated to assess cumulative survival rates in ESCC patients by gender and by the concomitance of metabolic syndrome in both genders. Given the gender-specific differences in demographic and clinical profiles, Kaplan-Meier estimates further revealed that female patients with ESCC had significantly longer median survival time (MST) than male patients (180-+ months vs. 80.7 months, Log-rank test: $P < 0.0001$) (Fig. 1A). In view of this striking difference, the prediction of preoperative metabolic syndrome and its single components for ESCC mortality was separately analyzed in males and females. As expected, the absence of metabolic syndrome before surgery was associated with longer MST than its presence in males (Fig. 1B) and females (Fig. 1C), and this association was more obvious in males (87.2 months vs. 39.2 months, Log-rank test: $P = 0.0042$) (Fig. 1B).

Considering the facts that ESCC mortality rate increases smoothly over time and the $\ln(-\ln(S(t)))$ is a linear function of $\ln(t)$ (here, t is survival time, and $S(t)$ is survival function), it is more appropriate to adopt the Weibull proportional hazards model for multivariate-adjusted survival analysis. After controlling for age, smoking, drinking, esophagus location, histological differentiation, tumor embolus, TNM stage and tumor size, the HR for ESCC mortality in patients with metabolic syndrome relative to patients without was statistically significant in males (HR = 1.45; 95% CI: 1.14–1.83; $P = 0.002$), but not in females (HR = 1.46; 95% CI: 0.92–2.31; $P = 0.107$) (Table 2). Further after additionally adjusting for gender in all patients, the HR was 1.38 (95% CI: 1.14–1.66; $P = 0.001$).

As for single metabolic components, the multivariate-adjusted HRs were significant for hyperglycemia (HR = 1.98; 95% CI: 1.68–2.33; $P < 0.001$) and dyslipidemia (HR = 1.41; 95% CI: 1.20–1.65; $P < 0.001$) in males and for hyperglycemia (HR = 1.76; 95% CI: 1.23–2.51; P =

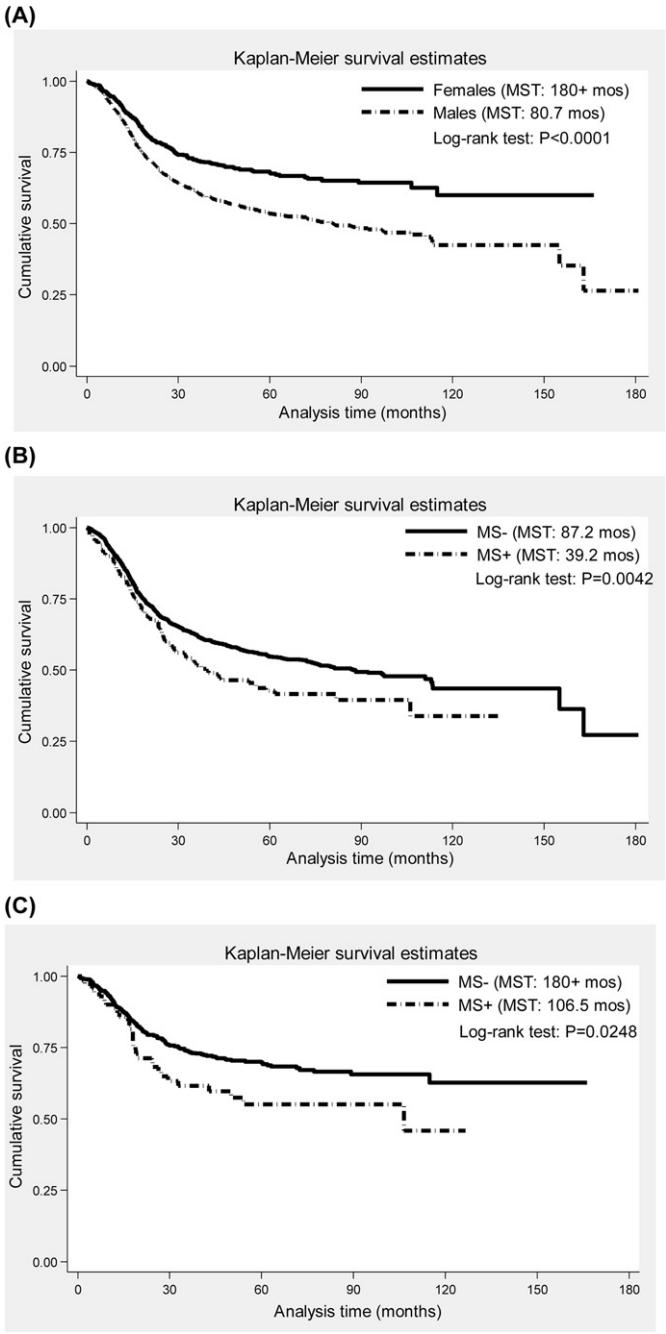

Fig. 1. Kaplan-Meier survival curves by gender (A) and the concomitance of metabolic syndrome in males (B) and females (C) for esophageal squamous cell carcinoma mortality. *Abbreviations*: MST, median survival time.

0.002) in females, after additionally adjusting for body mass index (Table 2). In all patients, the multivariate-adjusted HRs were significant only for hyperglycemia (HR = 2.00; 95% CI: 1.75–2.28; P < 0.001) and dyslipidemia (HR = 1.43; 95% CI: 1.26–1.63; P < 0.001) after additionally adjusting for gender.

In addition, the trend and the impact of metabolic risk factors including hyperglycemia or not on ESCC mortality are presented in Fig. 2. After treating ESCC patients without metabolic syndrome as a reference group, patients carrying one, two, three and four metabolic risk factors had a significant graded increase of multivariate-adjusted HRs in males (HR = 1.28, 1.69, 1.85 and 2.69, P = 0.017, <0.001, <0.001 and <0.001, respectively) after adjusting for age, smoking, drinking, esophagus location, histological differentiation, tumor embolus, TNM stage and tumor size, whereas this increase retained nonsignificant and showed no specific trends in females (Fig. 2A). In view of the leading impact of preoperative hyperglycemia on ESCC mortality, analysis based on the other three metabolic risk factors is displayed in Fig. 2B. The increasing trend was weakened in males, while significance was still identified in patients carrying one and three metabolic risk factors (multivariate-adjusted HR = 1.32 and 1.71, P = 0.002 and 0.013, respectively).

As shown in Table 2, analyzing metabolic relevant risk factors on a continuous scale found that in males per 10 mmHg increment in systolic and diastolic blood pressure was respectively associated with an 8% (HR = 1.08; 95% CI: 1.03–1.12; P = 0.001) and 12% (HR = 1.12; 95% CI: 1.04–1.21; P = 0.003) increased risk for ESCC mortality after adjusting for age, smoking, drinking, body mass index, esophagus location, histological differentiation, tumor embolus, TNM stage and tumor size. Likewise for fasting blood glucose, the multivariate-adjusted HR per 1 mmol/L increment was 1.09 (95% CI: 1.06–1.12; P < 0.001). In contrast, there was an 18% reduced risk (multivariate-adjusted HR = 0.82; 95% CI: 0.75–0.90; P < 0.001) per 0.42 mmol/L increment in high-density lipoprotein cholesterol. In females, only fasting blood glucose retained marginally significant with per 1 mmol/L increment corresponding to a 7% (multivariate-adjusted HR = 1.07; 95% CI: 1.02–1.12; P = 0.011) increased risk.

3.4. Survival Tree Analyses

Depicted in Figs. 3 and 4 are survival trees on the basis of metabolic risk factors along with clinicopathologic characteristics and the corresponding Kaplan-Meier curves in males and females, respectively. In fact, tree-structured survival analysis can better evaluate the prognostic value of single metabolic risk factors by determining the optimal cutoff values, which can divide patients into groups with the maximal median follow-up time difference. In both genders, the top splitting factor was TNM stage, followed by regional LNM. For instance, patients with TNM stage I or II had significantly longer median follow-up time in males (49.3 vs. 26.2 in months, Fig. 3A) and females (52.8 vs. 26.8 in months, Fig. 4A) than in patients with TNM stage III (both P < 0.001). Specifically in males, fasting blood glucose and systolic blood pressure were metabolic prognostic factors that can split patients into groups with distinct follow-up time periods, while in females the prognostic factors included low-density lipoprotein cholesterol and diastolic blood pressure. Based on the tree nodes containing more than 100/50 patients in males/females, the validity of tree-structured survival analysis was further confirmed by Kaplan-Meier curves (Figs. 3B and 4B).

3.5. Subgroup Analyses

Considering the crucial roles of TNM stage and regional LNM in above tree-structured survival analyses, the prediction of metabolic risk factors for ESCC mortality was stratified by the two clinicopathologic characteristics (Table 3). The multivariate-adjusted HR of metabolic syndrome was significant in male patients with TNM stage I or II (HR = 1.59; 95% CI: 1.05–2.41; P = 0.029) and positive regional LNM (N1–N3) (HR = 1.42; 95% CI: 1.10–1.83; P = 0.008) after adjusting for age, smoking and drinking, while no significance was noticed in females. For single metabolic components, both hyperglycemia and dyslipidemia were significantly associated with ESCC mortality in males, independent of obesity and irrespective of TNM stage or regional LNM, and the prediction was more obvious for hyperglycemia. In contrast to females, the association of hyperglycemia with ESCC mortality was significant in patients with TNM stage I or II (HR = 1.92; 95% CI: 1.03–3.58; P = 0.040) and negative regional LNM (HR = 2.26; 95% CI: 1.28–3.98; P = 0.005) after adjusting for age, smoking, drinking and body mass index.

Table 2
Metabolic syndrome and its single components associated with esophageal squamous cell carcinoma mortality.

Metabolic risk factors	HR; 95% CI; P*	
	Males	Females
Metabolic syndrome	1.45; 1.14–1.83; 0.002	1.46; 0.92–2.31; 0.107
Obesity	0.90; 0.72–1.12; 0.333	1.04; 0.71–1.52; 0.848
Hyperglycemia	1.98; 1.68–2.33; <0.001	1.76; 1.23–2.51; 0.002
Hypertension	1.17; 0.97–1.40; 0.101	0.90; 0.60–1.34; 0.590
Dyslipidemia	1.41; 1.20–1.65; <0.001	1.19; 0.84–1.69; 0.331
Relevant risk factors in continuous scales		
BMI (per 2.9/3.3 kg/m^2 in males/females)	1.00; 0.93–1.09; 0.907	1.03; 0.87–1.22; 0.713
SBP (per 10 mmHg in both genders)	1.08; 1.03–1.12; 0.001	1.05; 0.99–1.16; 0.304
DBP (per 10 mmHg in both genders)	1.12; 1.04–1.21; 0.003	1.14; 0.97–1.34; 0.112
Fasting blood glucose (per 1 mmol/L in both genders)	1.09; 1.06–1.12; <0.001	1.07; 1.02–1.12; 0.011
TG (per 0.9/0.83 mmol/L in males/females)	1.05; 0.98–1.13; 0.154	0.94; 0.77–1.16; 0.581
TC (per 1 mmol/L in both genders)	1.00; 0.93–1.08; 0.911	0.99; 0.84–1.17; 0.915
HDLC (per 0.42 mmol/L in both genders)	0.82; 0.75–0.90; <0.001	0.95; 0.79–1.14; 0.574
LDLC (per 1 mmol/L in both genders)	1.01; 0.93–1.10; 0.743	0.96; 0.79–1.16; 0.680

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol.

* P was calculated by the Weibull proportional hazards regression model after adjusting for age, smoking, drinking, esophagus location, histological differentiation, tumor embolus, TNM stage, tumor size for metabolic syndrome, obesity, BMI, and additionally adjusting for BMI (continuous scale) for the other risk factors.

4. Discussion

On the basis of 2396 ESCC patients who underwent three-field lymphadenectomy from the FIESTA study (Hu et al., 2016a,b; Hu et al., 2017; Peng et al., 2016), we assessed the gender-specific prediction of preoperative metabolic syndrome and its single components for esophageal cancer mortality over a 15-year follow-up period. The key finding of the present study is that preoperative metabolic syndrome was identified as a significant independent predictor of ESCC mortality in male patients, and this effect was largely mediated by glyeolipid metabolism disorder. In addition, the predictive utility of metabolic components, fasting blood glucose in particular, for ESCC mortality was contingent on TNM stage and regional LNM and was independent of obesity. To the best of our knowledge, this is so far the first prospective cohort study that has evaluated the preoperative prognosis of metabolic syndrome for esophageal cancer.

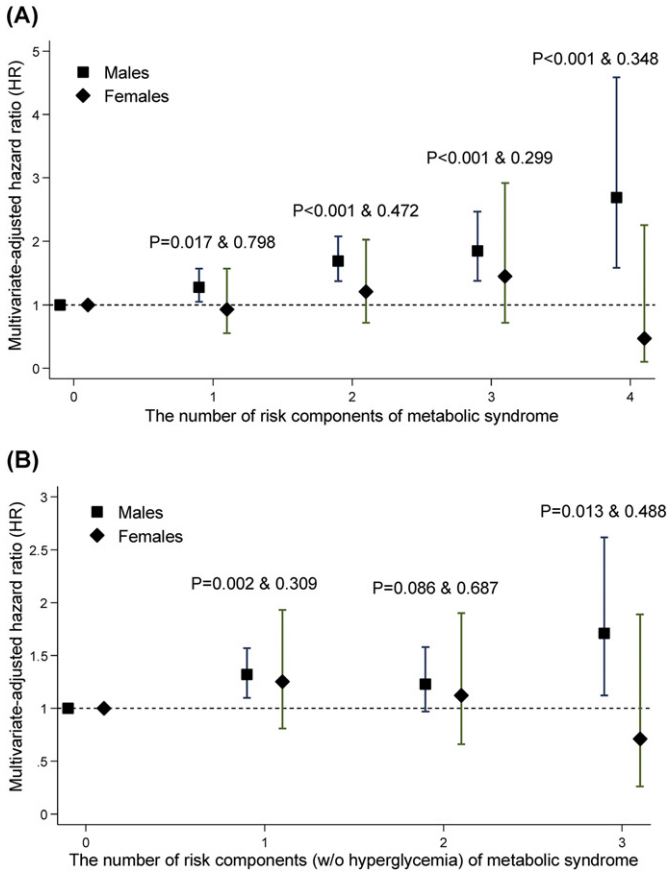

Fig. 2. The gender-specific changes of effect-size estimates with the increase of single metabolic risk factors* with (A) and without (B) hyperglycemia for esophageal squamous cell carcinoma mortality. *Metabolic risk factors include obesity, hyperglycemia, hypertension and dyslipidemia according to the diagnostic criteria proposed by the Chinese Diabetes Society in 2004. P was calculated by the Weibull proportional hazards regression model after adjusting for age, smoking, drinking, esophagus location, histological differentiation, tumor embolus, TNM stage and tumor size.

Several large epidemiologic studies have confirmed the predisposition of metabolic risk factors to the development of several malignancies, including esophageal cancer (Cowey and Hardy, 2006; Lin et al., 2015; Borena et al., 2012; Sponholtz et al., 2016; Lindkvist et al., 2014). However, evidence is sparse in medical literature supporting a contributing role of metabolic abnormalities in the prognosis of esophageal cancer. It is hence tempting for us to speculate that preoperative metabolic syndrome may represent a high-risk status for poor overall survival in esophageal cancer patients. In this respect, only one study was identified in current medical literature by Wen et al. who argued against this speculation after retrospectively reviewing 596 ESCC patients after surgery and found that patients with concomitant metabolic syndrome had a 41% reduced risk of mortality relative to patients with normal metabolic conditions (Wen et al., 2016). In addition, they found that nearly all single components of metabolic syndrome were favorable, albeit nonsignificant, prognostic factors (Wen et al., 2016). Our current findings based on a larger prospective cohort with a longer follow-up period yet completely subverted their conclusions, by showing that the concomitance of metabolic syndrome before surgery was significantly associated with an elevated risk of ESCC mortality, especially in males, wherein the biggest impact on this association rested with two metabolic components, hyperglycemia and dyslipidemia. What the present study and the Wen et al.'s study had in common is that the two studies were conducted in populations of exclusively Chinese descent and from the high incidence area of esophageal cancer (the Fujian-Guangdong region), and most importantly they shared similar diets and lifestyles (such as the consumption of pickled and high-salt foods). China has the highest incidence of esophageal cancer especially ESCC, and the major contributing risk factors include low intake of fruits and vegetables, poor nutritional status and drinking beverages at high temperatures (Wu et al., 2009; Zou et al., 2002; Tang et al., 2014). Hence, the patient cohorts of two studies were homogeneous with

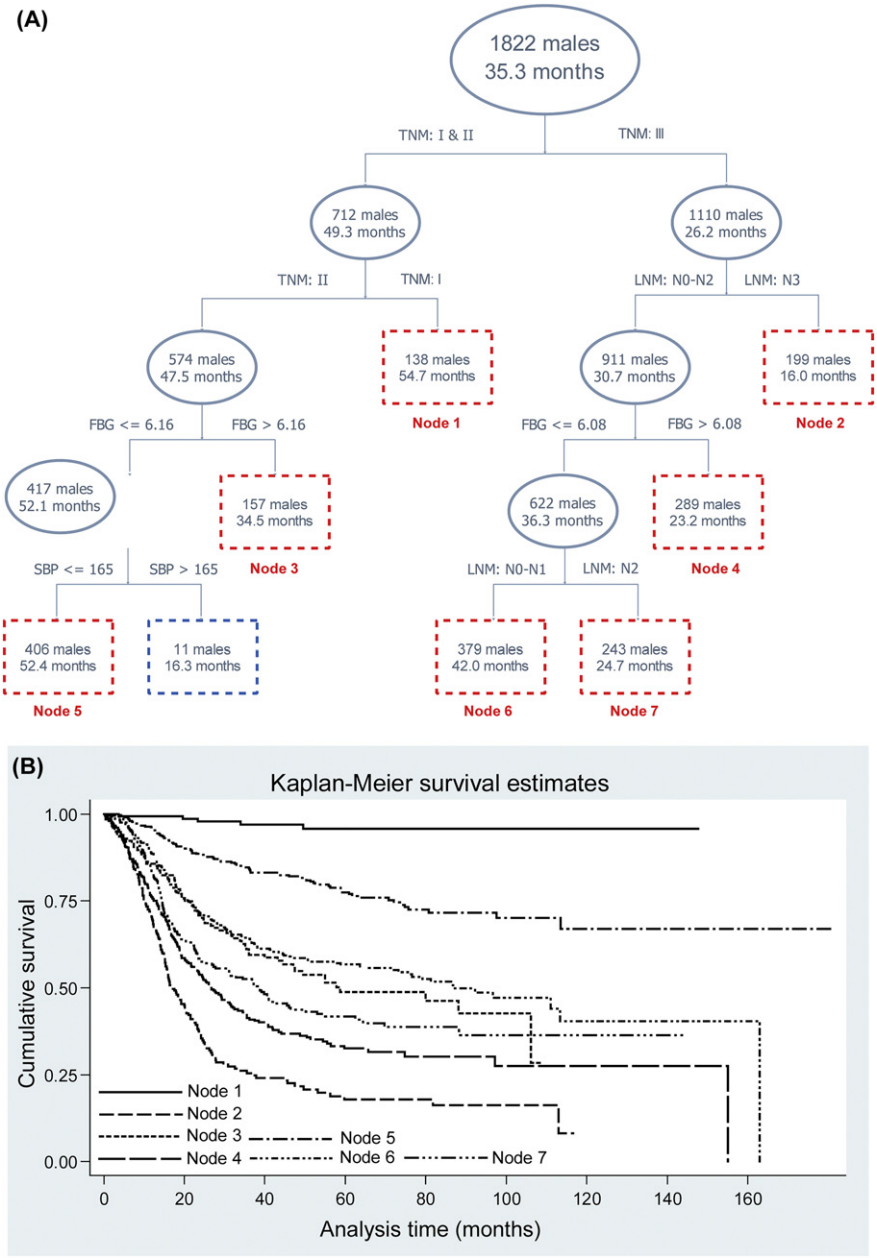

Fig. 3. Tree-structured survival analysis of metabolic risk factors along with clinicopathologic characteristics (A) and Kaplan-Meier survival curve of the generated nodes with sufficient power (B) for esophageal squamous cell carcinoma mortality in males. *Abbreviations*: TNM, tumor node metastasis; LNM, lymph node metastasis; FBG, fasting blood glucose (in mmol/L); SBP, systolic blood pressure (in mmHg). In panel A, the upper number in the box represents the number of ESCC patients and the lower number represents median follow-up time.

respect to ethnicity and geographic region, which minimized internal inconsistency.

By contrast, what makes the two studies different lies in study design (the present study vs. the Wen et al. study: prospective vs. retrospective design), sample size (2396 vs. 596 ESCC patients) and gender-specific exploration (with vs. without), which might at least in part lend credence to the completely opposite conclusions. Indeed, the cumulative survival rates differed strikingly between genders, as well as by the presence of metabolic syndrome in both genders, as illustrated in Fig. 1A. On the other hand, the lack of association between metabolic syndrome and ESCC mortality in females might be attributable to the confounding impact of menopausal status. We could not obtain information about menopausal status in females, and therefore our analysis remained unadjusted for this confounder. Instead as an approximation, we restricted the prognostic analysis to female patients aged over 50 years, and interestingly found that metabolic syndrome was marginally associated with an elevated risk of ESCC mortality (HR = 1.62; 95% CI: 1.00–2.61; 0.049) after adjusting for baseline and clinicopathologic characteristics, likely due to the inadequate sample size involved. Moreover, the present data do not allow us to further interrogate the impact of menopausal estrogens in the prognosis of esophageal cancer pending more compelling data are made available. Elucidating the underlying divergences between the two studies is beyond the scope of this study; however our conclusion of proposing preoperative metabolic syndrome as an independent prognostic factor for ESCC mortality in male patients seems clinically and epidemiologically more plausible.

Specifically in this study, the significant prediction of metabolic syndrome for ESCC mortality was observed to be largely mediated by hyperglycemia and dyslipidemia. In support of this view, a previous meta-analysis of 17 observational studies documented that males with diabetes may have a modestly increased risk of esophageal cancer,

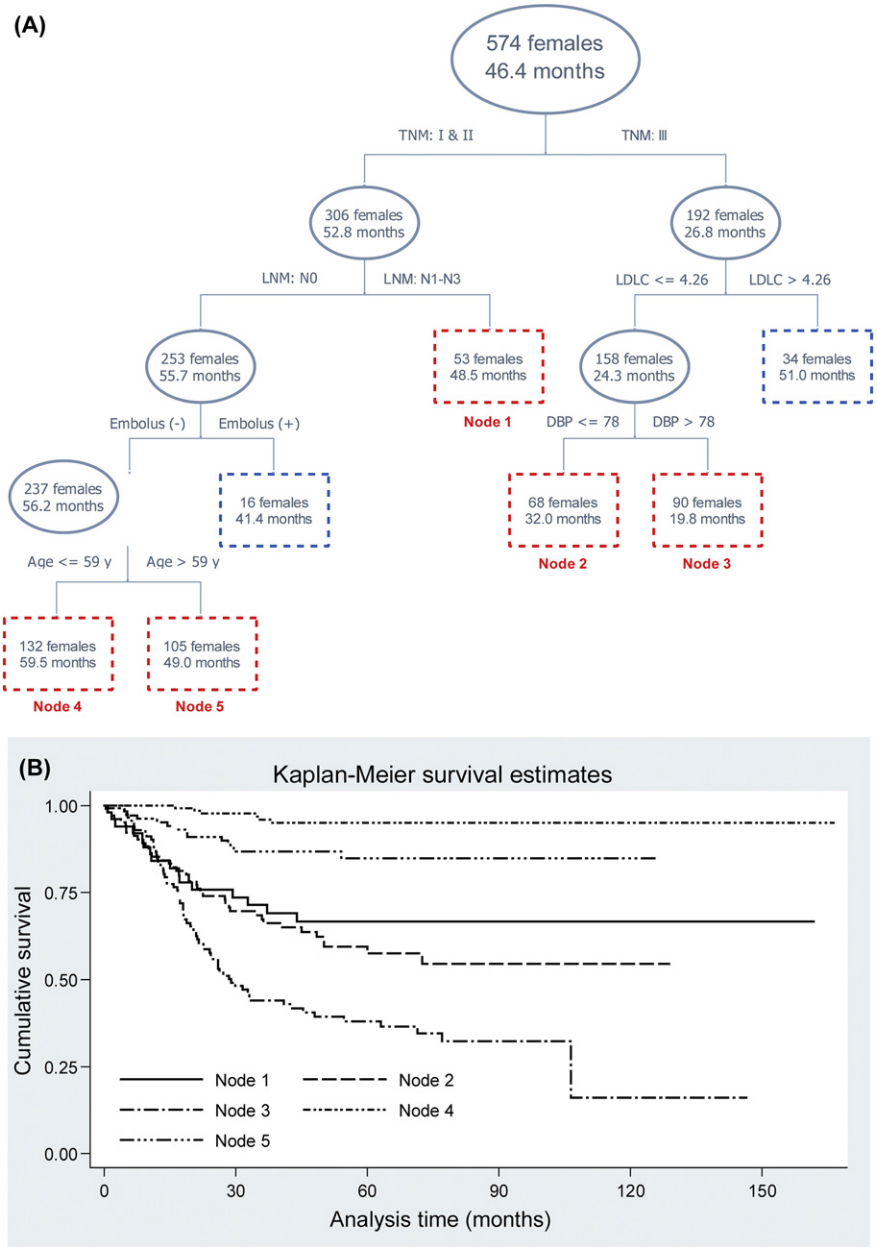

Fig. 4. Tree-structured survival analysis of metabolic risk factors along with clinicopathologic characteristics (A) and Kaplan-Meier survival curve of the generated nodes with sufficient power (B) for esophageal squamous cell carcinoma mortality in females. *Abbreviations*: TNM, tumor node metastasis; LNM, lymph node metastasis; LDLC, low-density lipoprotein cholesterol (in mmol/L); DBP, diastolic blood pressure (in mmHg). In panel A, the upper number in the box represents the number of ESCC patients and the lower number represents median follow-up time.

while it wasn't the case for diabetic females (Chen et al., 2016), the gender-specific relation between diabetes and esophageal cancer risk in parallel with that between preoperative hyperglycemia and ESCC mortality observed in the present study. However, recent large cohort studies argued against this claim by identifying the presence of diabetes as a protective factor in predisposition to esophageal cancer (Atchison et al., 2011; Lai et al., 2013; Gong et al., 2016). Especially in about 4.5 million black and white U.S. veterans, the presence of diabetes was associated with a 23% reduced risk of developing esophageal cancer, and this association was independent of obesity and was more obvious in black males with a 46% reduced risk (Atchison et al., 2011). It is also worth noting that in a retrospective chart review of 109 ESCC patients by Ito et al. who demonstrated that hyperglycemia 3 days after surgery was a predictive factor of postoperative infections (Ito et al., 2014). By contrast, there is a paucity of information on the association of dyslipidemia with the risk or the prognosis of esophageal cancer. Actually in the present study, 12 patients died of postoperative complications before hospital discharge (7 cases of pulmonary infection, 3 cases of diabetic ketoacidosis and 2 cases of massive hemorrhage), and 5 of them suffered from metabolic syndrome, which led us to speculate that the concomitance of preoperative metabolic syndrome may be associated with a higher incidence rate of postoperative complications. Such a high rate and resultant severe consequences after lymphadenectomy for esophageal cancer have long been a tough problem constantly obsessing global thoracic surgeons. It is encouraging to strengthen the clinical management of preoperative metabolic syndrome in patients with esophageal cancer. On the basis of prior evidence and the present findings, we conclude that preoperative metabolic syndrome largely mediated by glyeolipid metabolism disorder is an independent prognostic predictor for ESCC mortality in male patients. As a reasonable extension, our findings further reinforced that the predictive utility of glyeolipid metabolism disorder depended on TNM stage and regional LNM. Although

Table 3
Metabolic syndrome and its single components associated with esophageal squamous cell carcinoma mortality by TNM stage and regional LNM.

Metabolic risk factors	HR; 95% CI; P*	
	Males	Females
TNM stage I or II		
Metabolic syndrome	1.59; 1.05–2.41; 0.029	1.08; 0.45–2.58; 0.870
Obesity	0.98; 0.66–1.45; 0.913	0.51; 0.21–1.21; 0.125
Hyperglycemia	2.42; 1.76–3.34; <0.001	1.92; 1.03–3.58; 0.040
Hypertension	1.38; 0.98–1.94; 0.065	0.64; 0.31–1.32; 0.226
Dyslipidemia	1.48; 1.09–2.03; 0.013	1.12; 0.60–2.09; 0.721
TNM stage III		
Metabolic syndrome	1.26; 0.98–1.63; 0.069	1.38; 0.86–2.23; 0.186
Obesity	0.86; 0.68–1.09; 0.219	1.14; 0.78–1.67; 0.489
Hyperglycemia	1.79; 1.51–2.11; <0.001	1.38; 0.96–2.00; 0.083
Hypertension	1.09; 0.90–1.32; 0.401	0.97; 0.64–1.45; 0.871
Dyslipidemia	1.41; 1.20–1.66; <0.001	1.04; 0.73–1.48; 0.833
Regional LNM (−)		
Metabolic syndrome	1.24; 0.83–1.84; 0.293	1.17; 0.52–2.64; 0.702
Obesity	0.84; 0.58–1.21; 0.339	0.55; 0.26–1.18; 0.126
Hyperglycemia	2.12; 1.61–2.79; <0.001	2.26; 1.28–3.98; 0.005
Hypertension	1.17; 0.86–1.59; 0.316	0.74; 0.37–1.44; 0.372
Dyslipidemia	1.51; 1.16–1.97; 0.002	1.06; 0.59–1.89; 0.852
Regional LNM (+)		
Metabolic syndrome	1.42; 1.10–1.83; 0.008	1.38; 0.84–2.28; 0.204
Obesity	0.86; 0.67–1.10; 0.241	1.39; 0.94–2.07; 0.102
Hyperglycemia	1.90; 1.59–2.26; <0.001	1.34; 0.91–1.98; 0.138
Hypertension	1.12; 0.92–1.37; 0.267	0.91; 0.59–1.40; 0.667
Dyslipidemia	1.48; 1.24–1.76; <0.001	1.18; 0.82–1.70; 0.380

Abbreviations: TNM, tumor node metastasis; LNM, lymph node metastasis; HR, hazard ratio; 95% CI, 95% confidence interval.

* P was calculated by the Weibull proportional hazards regression model after adjusting for age, smoking and drinking for metabolic syndrome, obesity, and additionally adjusting for body mass index (continuous scale) for the other risk factors.

future functional studies are necessary to fully unravel the underlying biological mechanisms of observed predictions, our findings require further external validation in sufficiently powered epidemiological studies, especially utilizing a prospective and long-term follow-up design.

Several limitations should be kept in mind when evaluating our findings. First, other anthropometric indexes of obesity such as waist and hip circumferences were not available for study patients, which precluded the comparisons of different official definitions of metabolic syndrome for esophageal cancer survival. Instead, to be more compatible with Chinese physical characteristics, we have adopted the criteria proposed by the Chinese Diabetes Society in 2004 to define metabolic syndrome (Association, 2004). Second, data on fasting insulin were unavailable for us as insulin resistance is a hallmark of metabolic syndrome and may offer mechanistic insights in light of its relevance to other GI tract tumors. In addition, data on drug regimens such as metformin, statins were also not available, which precluded us to explore their contributory or confounding roles in cancer-related mortality. Third, all study patients were consecutively enrolled from a mono-center, and our findings could better be generalized pending consistently validated in other cohorts. Fourth, the findings presented in this study cannot be directly extrapolated to the general populations as only patients who received surgery for esophageal cancer were eligible for inclusion and the 5-year survival rate of 52.15% in the present study was remarkably higher than that of general populations (around 20%) (Zeng et al., 2015; Tseng et al., 2015). Fifth, although this is so far the largest prospective cohort for ESCC, the number of patients diagnosed with EAC or esophageal neuroendocrine carcinomas is extremely small, limiting further comparative analyses. Future studies involving large samples specifically designed to examine the prognosis of metabolic syndrome in patients with these two rare types are warranted.

Taken together, via a prospective analysis of 2396 ESCC patients, our findings demonstrate that preoperative metabolic syndrome was a significant independent predictor of ESCC mortality in male patients, and this effect was largely mediated by glyeolipid metabolism disorder. What's more, our survival tree and subgroup analyses further demonstrated that the predictive ability of metabolic components, fasting blood glucose in particular, for ESCC mortality was contingent on TNM stage and regional LNM and was independent of obesity. On the basis of these findings, we believe that early control and management of metabolic syndrome, especially keeping glucose and lipids within normal physiological ranges, will be essential to improve the prognosis of ESCC patients after surgery.

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Specific Author Contributions

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

Conflict of Interest Statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2017.01.035.

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