

ORIGINAL ARTICLE

Clinical characteristics and survival of 5283 esophageal cancer patients: A multicenter study from eighteen hospitals across six regions in China

Yutong He¹ | Di Liang¹ | Lingbin Du² | Tiantian Guo¹ | Yanyu Liu¹ |
Xibin Sun³ | Ning Wang⁴ | Min Zhang⁵ | Kuangrong Wei⁶ | Baoen Shan¹ |
Wanqing Chen⁷

¹ Cancer Institute, the Fourth Hospital of Hebei Medical University/the Tumor Hospital of Hebei Province, Shijiazhuang, Hebei 050000, P. R. China

² Zhejiang Cancer Center, Hangzhou, Zhejiang 310000, P. R. China

³ Henan Cancer Hospital, Zhengzhou, Henan 450000, P. R. China

⁴ Beijing Cancer Hospital, Beijing 100021, P. R. China

⁵ Hubei Cancer Hospital, Wuhan, Hubei 430000, P. R. China

⁶ Zhongshan Cancer Hospital, Zhongshan, Guangdong 528400, P. R. China

⁷ National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing 100021, P. R. China

Correspondence

Wanqing Chen; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing 100021, P. R. China.

Email: chenwq@cicams.ac.cn

Funding information

The National Key Research and Development Program of China; National Natural Scientific Foundation of China

Abstract

Objective: This study aimed to investigate the potential determining epidemiological and clinical risk factors affecting the survival of esophageal cancer (EC) patients across multiple hospitals in China.

Methods: This was a multicenter study comprising of newly diagnosed EC cases from Beijing, Hebei, Henan, Hubei, Zhejiang, and Guangdong Province of China. Their baseline characteristics and treatment methods data were collected from their medical records. The EpiData software was used for data quality control. The Kaplan-Meier method was used to estimate their overall survival (OS), and the Cox's proportional hazard regression model was used to estimate hazard ratios (HR) and 95% confidence interval (CI).

Results: The 3- and 5-year OS rates of the 5283 investigated EC patients were 49.98% and 39.07%, respectively. Their median survival was 36.00 months. The median survival time of females was longer than that of males (females vs. males: 45.00 vs. 33.00, $P < 0.001$). The 5-year OS rate of patients who never-smoked was higher than that of smokers (never-smokers vs smokers: 40.73% vs. 37.84%, $P = 0.001$). There was no significant difference in the 5-year OS rate between

List of abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; EAC, esophageal adenocarcinoma; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; FHC, family history of any cancer; FHEC, a family history of EC; HIS, health information system; HR, hazard ratio; ICD-O-3, the International Classification of Diseases for Oncology, Third Edition; NCCN, by the National Comprehensive Cancer Network; OS, overall survival; PSM, propensity score-matched

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drinkers and never-drinkers (drinkers vs never-drinkers: 34.22% vs. 29.65%, $P = 0.330$). In multivariate analysis, pathological stage (stage II: HR = 1.80, 95% CI = 1.40-2.31; stage III: HR = 2.62, 95% CI = 2.06-3.34; stage IV: HR = 3.90, 95% CI = 2.98-5.09), poor differentiation/undifferentiated (HR = 1.34, 95% CI = 1.11-1.63), not married status (HR = 2.45, 95% CI = 1.49-4.04), production and service personnel (HR = 1.36, 95% CI = 1.01-1.83) and farming/fishing (HR = 1.40, 95% CI = 1.12-1.76) were independent prognostic risk factors for poor EC survival. Tumors in the thoracic or abdominal part of the esophagus, female and family history of any cancer were independent factors predictive of a good EC OS.

Conclusion: Gender, marital status, occupation, family history of any cancer, tumor topographical site, differentiation status, and pathological stage were associated with the survival rate of EC. This study reveals important clinical characteristics of esophageal cancer patients in China and provides helpful information for their clinical management and surveillance.

KEYWORDS

esophageal cancer, overall survival, epidemiology, lifestyle, clinical factors, risk factors, multi-center study

1 | INTRODUCTION

Esophageal cancer (EC) is one of the most common gastrointestinal malignancies worldwide. The latest global statistics showed that there were 572,000 new EC cases and 509,000 EC-related deaths worldwide in 2018, ranking it as seventh and sixth in these respective categories [1]. According to the newly published 2018 China Cancer Report [2], the number of newly diagnosed EC cases in China was 258,000 and was ranked as the sixth most common incidence cancer type. EC was ranked fourth in terms of the number of related deaths, with 193,000 registered deaths. The incidence of EC varies from high- to low-incidence areas. For instance, Cixian had a high incidence of EC ($80.12/10^5$), which had a higher incidence rate by 4.16-fold than the national level ($19.24/10^5$) [3]. There are two main pathological types of EC: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC is the most common histological type in developing countries, such as China [4, 5]. The main treatments for EC are surgical resection, radiotherapy, and chemotherapy. Although great progress has been made in the treatment of EC, its prognosis is still poor, with a 5-year survival rate below 25% [6].

Many studies related to EC survival in recent years mainly focused on treatment methods including surgery [6], radiotherapy [7], and chemotherapy [8]. For instance, Spence et al [9] found that low-dose aspirin usage did not increase the survival of EC patients. In a retrospective study by Gabriel et al [10], a total of 1309 EC patients

were stratified into two groups according to metastasized status and underwent either neoadjuvant chemoradiation plus surgery or surgery alone. The results suggested that the hazard ratio (HR) of clinically metastatic lymph node patients who underwent neoadjuvant chemoradiation with surgery was 0.52 (95% CI [confidence interval] = 0.42-0.66). There are limited studies that investigated the association between lifestyle factors, such as smoking, drinking, marriage, occupation, body mass index (BMI), blood type, family history of any cancer (FHC) [11-13], and the survival of patients with EC. However, the results were inconsistent with other reports. Pan et al [14] performed a meta-analysis, comprising of fourteen studies with a total of 4,823 cases, investigating the impact of BMI on EC survival. Their results showed that high BMI was an independent favorable factor (HR = 0.81; 95% CI = 0.73-0.89) in EAC patients. In contrast, among patients with ESCC, high BMI was associated with a worse prognosis (HR, 2.26; 95% CI = 1.29-3.24). In 2015, Wang et al [15] first studied the effect of ABO blood type on EC survival and found no relationship between blood type and EC survival. In contrast, Qin et al [16] analyzed 548 ESCC patients who underwent cytoreductive surgery and found that the 5-year overall survival (OS) rates for A, B, O, and AB blood type patients were 41.20%, 49.70%, 44.00%, and 29.80%, respectively. The HR for type AB was 2.58, which was higher than those for the non-AB blood types. However, most of these studies were single-center, and/or with limited sample sizes. Additionally, the relationship between EC survival and lifestyle factors remains debatable.

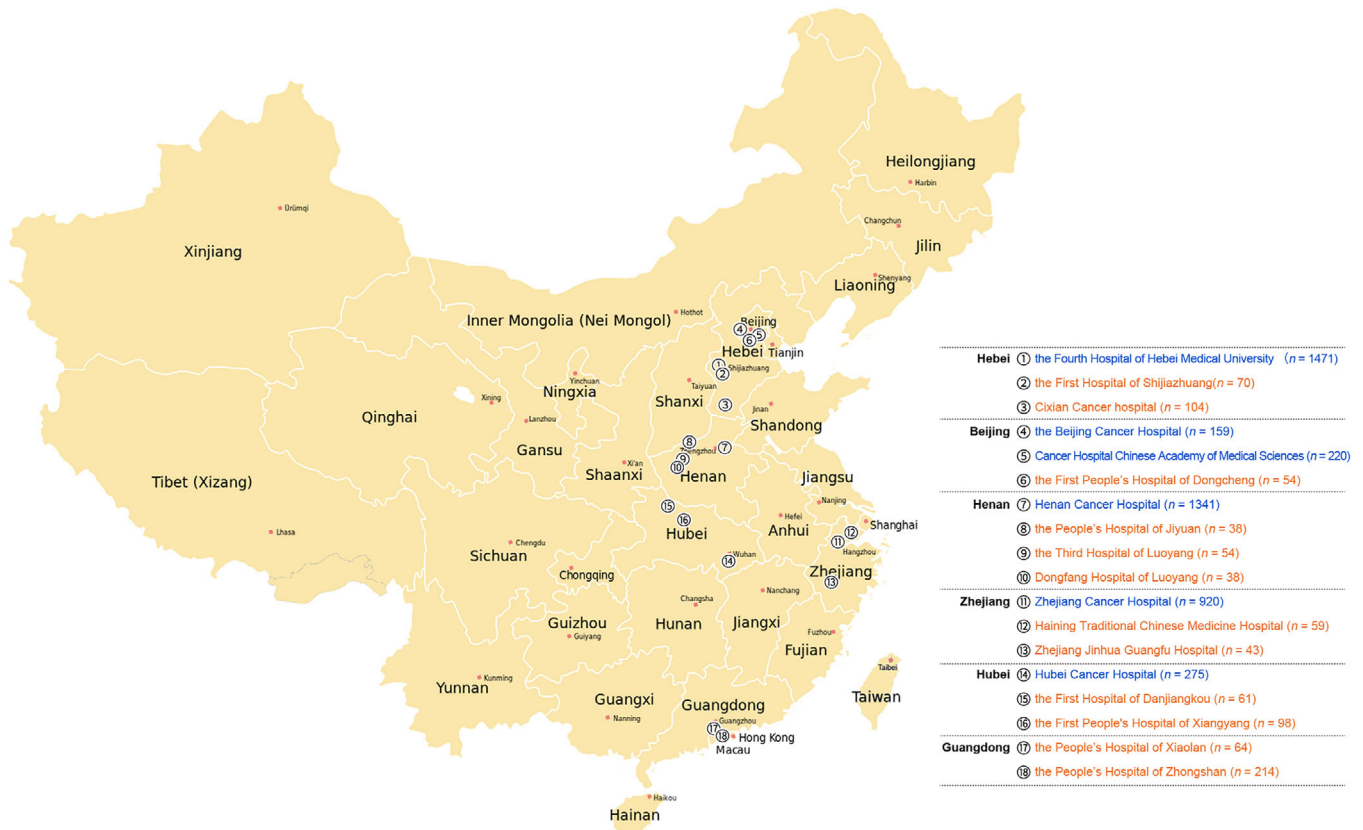


FIGURE 1 Distribution of the participating hospitals comprising of provincial (blue color), and municipal and county (orange color) hospitals

Therefore, the aim of this study was to use a large number of multicenter cases to determine the lifestyle and clinical risk factors related to the survival of EC patients in China. We believe that our findings could act as a guidance to help concerned authorities to improve the management of EC patients.

2 | METHODS AND MATERIALS

2.1 | Data

Data were collected from 6 provincial hospitals, 8 municipal hospitals, and 4 county hospitals across 6 regions in China which were from the Hebei Province (the Fourth Hospital of Hebei Medical University, the First Hospital of Shijiazhuang, and Cixian Cancer Hospital), Beijing (the Beijing Cancer Hospital, Cancer Hospital Chinese Academy of Medical Sciences, and the First People's Hospital of Dongcheng), Henan Province (Henan Cancer Hospital, the People's Hospital of Jiyuan, the Third People's Hospital of Luoyang, and Dongfang Hospital of Luoyang), Zhejiang Province (Zhejiang Cancer Hospital, Haining

Traditional Chinese Medicine Hospital, and Zhejiang Jinhua Guangfu Hospital), Hubei Province (Hubei Cancer Hospital, the First Hospital of Danjiangkou, and the First People's Hospital of Xiangyang), and Guangdong Province (the People's Hospital of Xiaolan, and the People's Hospital of Zhongshan) (Figure 1).

Trained investigators extracted information including the baseline characteristics (gender, age at diagnosis, marital status, occupation, height and weight at admission, blood type, history of smoking, alcohol consumption, and FHC), tumor-related information (pathological type, tumor topographical site, differentiation status, and pathological stage), treatment-related information (surgery, radiotherapy, chemotherapy, and targeted therapy). These data were extracted from patients' medical records using the health information system (HIS; Dayinjunhui company, Beijing, China). The tumor topographical site classification was coded as C15.0-C15.9 according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). C15.0, C15.1, C15.2 is defined as the cervical, thoracic, and abdominal esophagus respectively. C15.8 is defined as an overlapping lesion of the esophagus.

2.2 | Inclusion and exclusion criteria

Patients who met the following inclusion criteria were included: (1) newly diagnosed as esophageal cancer between January 1, 2011, and December 31, 2013; (2) their diagnosis and treatment criteria were in accordance with the esophageal cancer guidelines issued by the National Comprehensive Cancer Network (NCCN) 2010; and (3) their initial diagnosis and treatments were performed in the above-mentioned hospitals and had complete clinical records. The sampling of medical records in the provincial hospitals was performed as follows: the medical records of patients meeting the inclusion criteria were organized by month, and these records were randomly divided into two groups (odd numbers and even numbers) according to a random number table. There was no significant difference between the two groups in gender and age ($P > 0.05$). We included the even number group in the analysis. All the medical records from the municipal and county hospitals were included. Patients meeting the following criteria were excluded: (1) diagnosed with multiple primary or metastatic cancers; (2) non-local residents; and (3) received treatments such as surgery, radiotherapy, and/or chemotherapy prior to admission to the above-mentioned hospitals.

2.3 | Exposure evaluation and ascertainment

Based on the occupation information in the patients' medical records, occupations were divided into three categories: (1) enterprise personnel (e.g.: government officials, office clerks, technicians and so on), (2) production and service personnel (e.g.: factory workers, shop assistants and so on), and (3) fishing/farming (including those working in agriculture, forestry, animal husbandry, and fisheries).

BMI was calculated using the height and weight data retrieved at the time of the first diagnosis from the HIS medical record. According to the Asian standard, BMI was categorized into three groups, underweight ($< 18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}23 \text{ kg/m}^2$), and overweight or obese ($\geq 23 \text{ kg/m}^2$).

According to the admission records, the patients were defined as smokers if they had smoked ≥ 100 cigarettes in one's lifetime. Drinkers were defined as individuals who drank any alcoholic beverage one or more times per week. Patients who had any cancer or EC among first-degree or second-degree relatives were defined as patients having an FHC or a family history of EC (FHEC). The first-degree relatives included father, mother, or siblings; the second-degree relatives were restricted to grandparents, uncles,

and aunts. The pathological types and differentiation status in all patients were confirmed by pathological examination. EC patients were staged according to the 2007 American Joint Committee on Cancer (AJCC) TNM classification.

2.4 | Follow up

Patients were followed-up by passive and active methods until December 31, 2017, at every hospital. Active follow-ups were performed every 3 months by telephone calls or extracting re-admission information from the HIS system. Additionally, passive follow-ups were carried out by the staff of the hospital. They linked the patient records with the data of the local population-based cancer registries which could provide patients' survival status. The survival time of patients who were alive and censored was calculated from the date of diagnosis of EC until the last date of follow-up, and the survival time of patients who died was calculated from the date of diagnosis until the patients' death.

2.5 | Quality control

We standardized the format of the variables and used the EpiData software (version 3.1, EpiData Association, Denmark) to assess the quality of the data from all the eighteen participating hospitals. In a standardized format database, we selected 10% of the patients from each hospital with a random number table method. All the sampling medical records including the basic and clinical information were checked by two other staff members. The follow-up rate of all hospitals was ensured above 85%.

2.6 | Statistical analyses

All statistical analyses were performed using the SPSS software (version 21.0, SPSS Inc., Chicago, IL, USA) and the Stata software (version 12.0, StataCorp LLC, Texas, USA). The 3- and 5-year OS rates and median survival time were analyzed using the Kaplan-Meier method. Differences between the survival curves were determined using the log-rank test. Cox's proportional hazard regression models were used to calculate the HR and 95%CI in the univariate and multivariate survival analyses. A multivariate Cox's proportional hazard regression model was performed using the associated risk factors with P values less than 0.10 in univariate analysis. Two-sided P values < 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics of the investigated EC patients

A total of 5283 patients with EC were included in this study. As of December 31, 2017, there were 1333 (25.23%) patients who were still alive, 3158 (59.78%) deaths, and 2575 (48.74%) patients who had died due to EC. A total of 792 (14.99%) cases were lost to follow-up. The follow-up rate was 85.0%.

The age of the EC patients included in this study was between 16 and 90 years old, with a median age of 62 years old. A total of 3974 (75.22%) patients were male, and 1309 patients (24.78%) were female. Patients who were married accounted for 97.92% (5173/5283) of the entire cohort. In this study, 2615 (49.50%) were normal weight (18.5–23.0 kg/m²). There were 1518 (28.73%), 1502 (28.43%), 1438 (27.22%), and 455 (8.61%) patients with A, B, O, and AB blood types, respectively. In total, 2742 (51.90%) patients were smokers, and 2189 (41.43%) were drinkers. Patients with an FHC accounted for 20.63% (1090/5283) of the entire cohort.

The investigated tumor characteristics included tumor topographical site, pathological type, differentiation status, and pathological stage. As shown in Table 1, the thoracic part was the most common topographical site which accounted for 59.11% (3123/5283) of the entire cohort. Squamous cell carcinoma was the main pathological type which accounted for 85.29% (4506/5283) of the entire cohort. Moderately differentiated was the most common histological type; 32.22% (1702/5283). Advanced stage including pathological stage III and IV accounted for 41.72% (2204/5283).

3.2 | Survival and univariate analysis

The median follow-up time for the 5283 EC cases was 33.70 (range: 1.00, 100.63) months. The 3- and 5-year OS rate of all patients were 49.98% (95% CI = 48.60%-51.34%) and 39.07% (95% CI = 37.68%-40.46%), respectively. The median survival time for the investigated EC cases was 36.00 months (95% CI = 34.00-39.00). The 5-year OS of EC in provincial hospitals was 41.26%, which was higher than those in municipal and county hospitals (28.06%; Supplementary Table 1). The 5-year OS rates of patients who underwent surgery only, radiotherapy only, and chemotherapy only were 52.13%, 25.91%, and 24.33%, respectively.

As shown in Table 2, the median survival time of females was longer than that of males (male vs female: 33.00 vs. 45.00 months; $P < 0.001$). Smokers and drinkers had

TABLE 1 Clinical characteristics of the 5283 investigated esophageal cancer patients

Characteristics	No. of patients <i>n</i> (%)	No. of deaths <i>n</i> (%)
Total no. of cases	5283 (100)	3158 (100)
Gender		
Male	3974 (75.22)	2431 (76.98)
Female	1309 (24.78)	727 (23.02)
Age (years)		
≤44	117 (2.21)	61 (1.93)
45–54	860 (16.28)	477 (15.10)
55–64	2215 (41.93)	1268 (40.15)
65–74	1568 (29.68)	977 (30.94)
≥75	523 (9.90)	375 (11.87)
Marital status		
Married	5173 (97.92)	3082 (97.59)
Not married	93 (1.76)	66 (2.09)
Missing data	17 (0.32)	10 (0.32)
Occupation		
Enterprise personnel	502 (9.50)	253 (8.01)
Production and service personnel	565 (10.69)	290 (9.18)
Farming/fishing	3910 (74.01)	2390 (75.68)
Missing data	306 (5.79)	225 (7.12)
BMI (kg/m²)		
<18.5	381 (7.21)	241 (7.63)
18.5–23.0	2615 (49.50)	1553 (49.18)
≥23.0	1431 (27.09)	878 (27.80)
Missing data	856 (16.20)	486 (15.39)
Blood type		
A	1518 (28.73)	840 (26.60)
B	1502 (28.43)	943 (29.86)
O	1438 (27.22)	887 (28.09)
AB	455 (8.61)	270 (8.55)
Missing data	370 (7.00)	218 (6.90)
Smoking status		
Never-smoker	2489 (47.11)	1441 (45.63)
Smoker	2742 (51.90)	1677 (53.10)
Missing data	52 (0.98)	40 (1.27)
Drinking status		
Never-drinker	2250 (42.59)	1540 (48.77)
Drinker	2189 (41.43)	1423 (45.06)
Missing data	844 (15.98)	195 (6.17)
Family history of any cancer		
Absent	4115 (77.89)	2522 (79.86)
Present	1090 (20.63)	575 (18.21)
Missing data	78 (1.48)	61 (1.93)

(Continues)

TABLE 1 (Continued)

Characteristics	No. of patients <i>n</i> (%)	No. of deaths <i>n</i> (%)
Tumor topographical site		
Cervical part	575 (10.88)	352 (11.15)
Thoracic part	3123 (59.11)	1804 (57.12)
Abdominal part	895 (16.94)	545 (17.26)
Overlapping lesion of the esophagus	452 (8.56)	295 (9.34)
Missing data	238 (4.51)	162 (5.13)
Pathological type		
Squamous cell carcinoma	4506 (85.29)	2646 (83.79)
Adenocarcinoma	125 (2.37)	79 (2.50)
Adenosquamous carcinoma	67 (1.27)	44 (1.39)
Other types	161 (3.05)	109 (3.45)
Missing data	424 (8.03)	280 (8.87)
Differentiation status		
High differentiation	805 (15.24)	413 (13.08)
Moderate differentiation	1702 (32.22)	1006 (31.86)
Poor/Undifferentiated	1414 (26.77)	893 (28.28)
Missing data	1362 (25.78)	846 (26.79)
Pathological stage		
I	741 (14.03)	273 (8.64)
II	1413 (26.75)	753 (23.84)
III	1319 (24.97)	852 (26.98)
IV	885 (16.75)	659 (20.87)
Missing data	925 (17.51)	621 (19.66)

*Body mass index

comparatively lower median survival time than never smokers and non-drinkers. The 5-year OS rates of patients with A, B, O, and AB blood types were 44.01%, 36.28%, 36.59%, and 39.78%, respectively. However, the 3- and 5-year OS rates of patients with FHC were 56.34% and 46.36%, respectively, which were higher than those of patients without FHC (3-year OS: 48.55%; 5-year OS: 37.39%). The 5-year OS rates of patients with cancer in the thoracic esophagus were 41.26%, which were higher than those of patients with tumors in other topographical sites (cervical part, abdominal part and overlapping lesion of the esophagus). The 5-year OS rates of ESCC and EAC were 40.09% and 37.46%, respectively. The 5-year OS rate of pathological stage I was 61.90%. Supplementary Fig. S1-3 shows the survival curves stratified by different factors.

The factors associated with EC survival on univariate analysis are shown in Table 3. To further investigate the reasons for the higher survival rate of patients with an FHC, we analyzed the distributions of differentiation status and pathological stage based on the presence or

absence of FHC. Patients with FHC had a better survival rate than with patients without FHC ($P < 0.001$). Supplementary Table 2 shows that the proportion of patients with moderate and high differentiation status in the FHC group was 49.36%, which was higher than that of patients without FHC (46.88%). In addition, patients with FHC were more likely to have pathological stages I and II EC (44.22%) and the proportion of pathological stage I and II without FHC was 40.07% ($P = 0.064$). We also further analyzed the survival of patients with FHEC. The results were consistent with those for patients with FHC, in which the proportions of patients with and without FHEC with pathological stages I and II were 46.25% and 40.31%, respectively ($P = 0.027$; Supplementary Table 2)

3.2.1 | Stratified survival analysis by smoking status

We categorized the patients into never-smokers and smokers (current and former smokers) according to their history of smoking. The 5-year OS rate of patients who were never-smokers was 40.73%, which was higher than that in the smoker group (37.84%; $P = 0.001$). The 5-year OS rate of never-smokers with FHC was 50.36% (95% CI = 45.61%-54.90%), which was higher than that of smokers who had FHC (43.37%; 95% CI = 39.15%-47.50%; $P = 0.011$); and the 5-year OS rates of patients without FHC in the two groups were 38.50% and 36.40%, respectively ($P = 0.015$). In the never smoker group, the 5-year OS rates of patients with pathological stage III and IV were 34.18% and 28.78%, respectively; while they were 32.18% and 24.30% in the smoker group, respectively. The 5-year survival rates of patients with tumors in the cervical and thoracic parts were 38.73% and 42.36% in the never-smoker group, respectively, and in the smoker group, they were 33.12% and 40.30%.

In the never-smoker group, the median survival time of females was 46.00 (95% CI = 40.73-51.27) months, which was higher than that of males ($P = 0.001$). Patients with normal and high BMI lived longer than patients with lower BMI (median survival time: normal BMI: 42.00 months; high BMI: 36.00 months; lower BMI: 28.00 months; $P = 0.001$). ESCC patients survived longer than patients with other pathological types ($P = 0.003$). However, among smokers, there were no significant differences in survival based on gender, BMI, or pathological type. In the group of smokers, the median survival time for married patients were better than those for unmarried patients ($P = 0.008$). There was no significant difference in the survival of EC patients by blood type when stratified by smoking status (Supplementary Table 3).

TABLE 2 Overall survival rate and median survival time of the 5283 esophageal cancer patients

Characteristics	Overall survival rate (%; 95% CI)		Median survival time (months-95% CI)	P value ^a
	3-year	5-year		
All patients	49.98 (48.60-51.34)	39.07 (37.68-40.46)	36.00 (34.00-39.00)	
Age(year)				<0.001
≤44	54.31 (44.62-63.02)	46.32 (36.69-55.39)	44.00 (- ^{**})	
45-54	50.92 (47.46-54.26)	43.65 (40.17-47.07)	37.00 (29.69-44.32)	
55-64	52.28 (50.14-54.36)	41.30 (39.13-43.47)	40.00 (35.89-44.11)	
65-74	49.77 (47.24-52.24)	36.73 (34.21-39.25)	35.00 (31.26-38.74)	
≥75	38.28 (34.03-42.51)	27.49 (23.48-31.65)	22.00 (18.35-25.65)	
Gender				<0.001
Male	48.16 (46.57-49.72)	37.73 (36.14-39.32)	33.00 (30.74-35.26)	
Female	55.55 (52.76-58.24)	43.19 (40.34-46.01)	45.00 (39.78-50.22)	
Marital status				0.004
Married	50.09 (48.69-51.46)	39.26 (37.85-40.66)	36.00 (33.63-38.38)	
Not married	40.93 (30.71-50.87)	27.32 (17.23-38.04)	25.00 (14.24-35.76)	
Occupation				<0.001
Enterprise personnel	58.94 (54.46-63.13)	48.75 (44.05-53.27)	54.00 (43.67-64.33)	
Production and service personnel	55.67 (51.39-59.73)	47.73 (43.30-52.03)	49.00 (38.58-59.42)	
Farming/fishing	48.86 (47.25-50.44)	37.86 (36.27-39.46)	34.00 (31.60-36.40)	
BMI^{***} (kg/m²)				0.014
< 18.5	43.41 (38.29-48.41)	34.90 (29.87-39.98)	25.00 (19.68-30.32)	
18.5-23.0	50.03 (48.07-51.96)	39.85 (37.88-41.82)	36.00 (32.71-39.29)	
≥23.0	48.50 (45.83-51.12)	37.16 (34.52-39.79)	34.00 (30.23-37.77)	
Blood type				0.028
A	52.45 (49.86-54.97)	44.01 (41.39-46.60)	40.00 (34.12-45.89)	
B	49.88 (47.29-52.41)	36.28 (33.70-38.86)	36.00 (32.56-39.44)	
O	47.88 (45.24-50.47)	36.59 (33.95-39.23)	32.00 (28.47-35.53)	
AB	49.25 (44.50-53.82)	39.78 (35.05-44.46)	35.00 (26.85-43.15)	
Smoking status				0.001
Never-smoker	53.03 (51.01-55.00)	40.73 (38.68-42.77)	41.00 (37.46-44.54)	
Smoker	47.48 (45.57-49.36)	37.84 (35.93-39.74)	31.00 (28.25-33.75)	
Drinking status				0.330
Never-drinker	43.94 (41.84-46.02)	29.65 (27.67-31.65)	29.00 (27.09-30.91)	
Drinker	43.69 (41.57-45.78)	34.22 (32.14-36.31)	27.00 (24.81-29.19)	
Family history of any cancer				<0.001
Absent	48.55 (46.99-50.09)	37.39 (35.83-38.95)	33.00 (30.83-35.17)	
Present	56.34 (53.29-59.26)	46.36 (43.22-49.44)	51.00 (43.95-58.05)	
Family history of esophageal cancer				<0.001
Absent	49.25 (47.78-50.70)	38.13 (36.66-39.61)	35.00 (32.00-38.00)	
Present	57.74 (53.54-61.70)	48.32 (43.97-52.53)	55.00 (46.00-69.00)	
Tumor topographical site				<0.001
Cervical part	45.41 (41.21-49.51)	36.10 (31.90-40.30)	28.00 (22.74-33.26)	
Thoracic part	53.08 (51.29-54.84)	41.26 (39.43-43.07)	41.00 (37.73-44.27)	
Abdominal part	46.96 (43.60-50.25)	37.64 (34.27-40.99)	30.00 (25.32-34.68)	

(Continues)

TABLE 2 (Continued)

Characteristics	Overall survival rate (%; 95% CI)		Median survival time (months-95% CI)	P value*
	3-year	5-year		
Overlapping lesion of esophagus	43.11 (38.49-47.64)	35.39 (30.91-39.90)	24.00 (20.01-27.99)	
Pathological stage				<0.001
I	72.08 (68.65-75.21)	61.90 (58.08-65.49)	84.00 (59.95-108.05)	
II	58.69 (56.04-61.23)	46.60 (43.81-49.34)	52.00 (46.28-57.72)	
III	43.26 (40.52-45.97)	32.80 (30.10-35.52)	27.00 (24.45-29.55)	
IV	37.40 (34.18-40.63)	26.17 (23.23-29.20)	23.00 (20.37-25.63)	
Pathological type				0.008
Squamous cell carcinoma	50.75 (49.26-52.22)	40.09 (38.58-41.59)	38.00 (35.00-41.00)	
Adenocarcinoma	46.12 (36.80-54.93)	37.46 (28.28-46.61)	30.00 (20.00-54.00)	
Adenosquamous carcinoma	46.22 (34.00-57.58)	32.73 (21.54-44.37)	30.00 (15.00-42.00)	
Other types	43.19 (35.21-50.91)	28.09 (20.85-35.76)	29.00 (22.33-38.00)	
Differentiation status				<0.001
High differentiation	60.34 (56.00-64.39)	49.50 (45.01-53.83)	59.00 (50.33-67.67)	
Moderate differentiation	51.86 (48.83-54.81)	41.33 (38.25-44.39)	39.00 (33.17-44.83)	
Poor/Undifferentiated	47.41 (44.10-50.64)	35.98 (32.67-39.30)	29.00 (35.21-42.79)	

*P value for the 5-year OS of each subgroup

**95% CI can not be estimated

***Body mass index

3.2.2 | Stratified survival analysis by drinking

To further analyze the effect of drinking on the patients' survival, the patients were divided into two groups based on their drinking status. The median survival times of patients in the never drinker and drinker groups were 29.00 and 27.00 months, respectively ($P = 0.596$).

The 5-year OS rates of patients with low, normal, and high BMI in the never-drinker group were 35.02%, 28.60%, and 36.08% ($P = 0.011$), while the 5-year OS rates were 33.78%, 34.67%, and 37.67% ($P = 0.009$) in the drinkers' group, respectively. For patients in an advanced stage, the drinker group had a poorer prognosis than the never-drinker group. The median survival times of patients with pathological stage IV were 25.00 months in the never-drinker group, which corresponded to 15.00 months in the drinker group ($P < 0.001$). The median survival times of patients with poor differentiation/undifferentiated tumors in the never-drinker and drinker groups were 26.00 and 21.00 months ($P = 0.957$), respectively. There was no significant association between blood type, smoking or tumor topographical site, and EC survival in the never-drinker and drinker groups.

In the group of never drinkers, females had a better 5-year OS rate (33.04%, 95% CI = 29.96-36.15) than males

(27.04%, 95% CI = 24.49-29.65) (male vs. female: $P = 0.004$). A better 5-year survival rate was also observed in married patients ($P < 0.001$) compared with their counterparts. In the drinker's group, the median survival time of patients with FHC was 35 months, which was longer than that of patients without FHC ($P < 0.001$; Supplementary Table S4).

3.3 | Multivariate analysis of clinical characteristics, lifestyle factors and EC survival

Multivariate analyses indicated that advanced pathological stage (stage II: HR = 1.80, 95% CI = 1.40-2.31; stage III: HR = 2.62, 95% CI = 2.06-3.34; stage IV: HR = 3.90, 95% CI = 2.98-5.09), poor differentiation/undifferentiated (HR = 1.34, 95% CI = 1.11-1.63), not-married status (HR = 2.45, 95% CI = 1.49-4.04), production and service personnel (HR = 1.36, 95% CI = 1.01-1.83), farming/fishing (HR = 1.40, 95% CI = 1.12-1.76) were identified as independent prognostic factors for poor EC OS. Tumor topographical sites of EC was found to affect EC survival. The survival of EC patients whose tumor were located in the thoracic, abdominal, and overlapping part of the esophagus was better than those located in the cervical part ($P = 0.013$). Female (vs male, $P < 0.001$) and having FHC (vs absent

TABLE 3 Univariate and multivariate analyses demonstrating the association between clinical characteristics, lifestyle factors, and esophageal cancer survival

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95%CI)	<i>P</i> value	HR (95%CI)	<i>P</i> value
Gender		<0.001		<0.001
Male	1.00		1.00	
Female	0.84 (0.77-0.91)		0.67 (0.56-0.81)	
Age(years)		<0.001		
≤44	1.00			
45-54	1.15 (0.88-1.50)			
55-64	1.13 (0.87-1.46)			
65-74	1.26 (0.97-1.63)			
≥ 75	1.75 (1.34-2.30)			
Marital status		0.004		<0.001
Married	1.00		1.00	
Not married	1.43 (1.12-1.82)		2.45 (1.49-4.04)	
Occupation		<0.001		0.010
Enterprise personnel	1.00		1.00	
Production and service personnel	1.07 (0.90-1.26)		1.36 (1.01-1.83)	
Farming/fishing	1.27 (1.12-1.45)		1.40 (1.12-1.76)	
BMI[†] (kg/m²)		0.009		
< 18.5	1.00			
18.5-23.0	0.81 (0.71-0.93)			
≥23.0	0.86 (0.75-0.99)			
Blood type		0.038		
A	1.00			
B	1.13 (1.03-1.24)			
O	1.13 (1.03-1.24)			
AB	1.08 (0.94-1.23)			
Smoking status		0.001		
Never-smoker	1.00			
Smoker	1.13 (1.05-1.21)			
Drinking status		0.335		
Never-drinker	1.00			
Drinker	0.97 (0.90-1.04)			
Family history of any cancer		<0.001		<0.001
Absent	1.00		1.00	
Present	0.78 (0.71-0.85)		0.73 (0.61-0.87)	
Tumor topographical site		<0.001		0.013
Cervical part	1.00		1.00	
Thoracic part	0.83 (0.74-0.93)		0.65 (0.50-0.83)	
Abdominal part	0.98 (0.85-1.11)		0.72 (0.55-0.95)	
Overlapping lesion of esophagus	1.06 (0.90-1.23)		0.69 (0.51-0.94)	
Pathological type		0.002		
Squamous cell carcinoma	1.00			
Other types [‡]	1.24 (1.08-1.42)			

(Continues)

TABLE 3 (Continued)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Differentiation status		<0.001		0.010
High differentiation	1.00		1.00	
Moderate differentiation	1.27 (1.10-1.47)		1.19 (0.99-1.43)	
Poor/Undifferentiated	1.46 (1.26-1.69)		1.34 (1.11-1.63)	
Pathological stage		<0.001		<0.001
I	1.00		1.00	
II	1.60 (1.39-1.83)		1.80 (1.40-2.31)	
III	2.40 (2.09-2.75)		2.62 (2.06-3.34)	
IV	2.90 (2.52-3.34)		3.90 (2.98-5.09)	

*Other types included adenocarcinoma, adenosquamous carcinoma, and other types.

**Body mass index

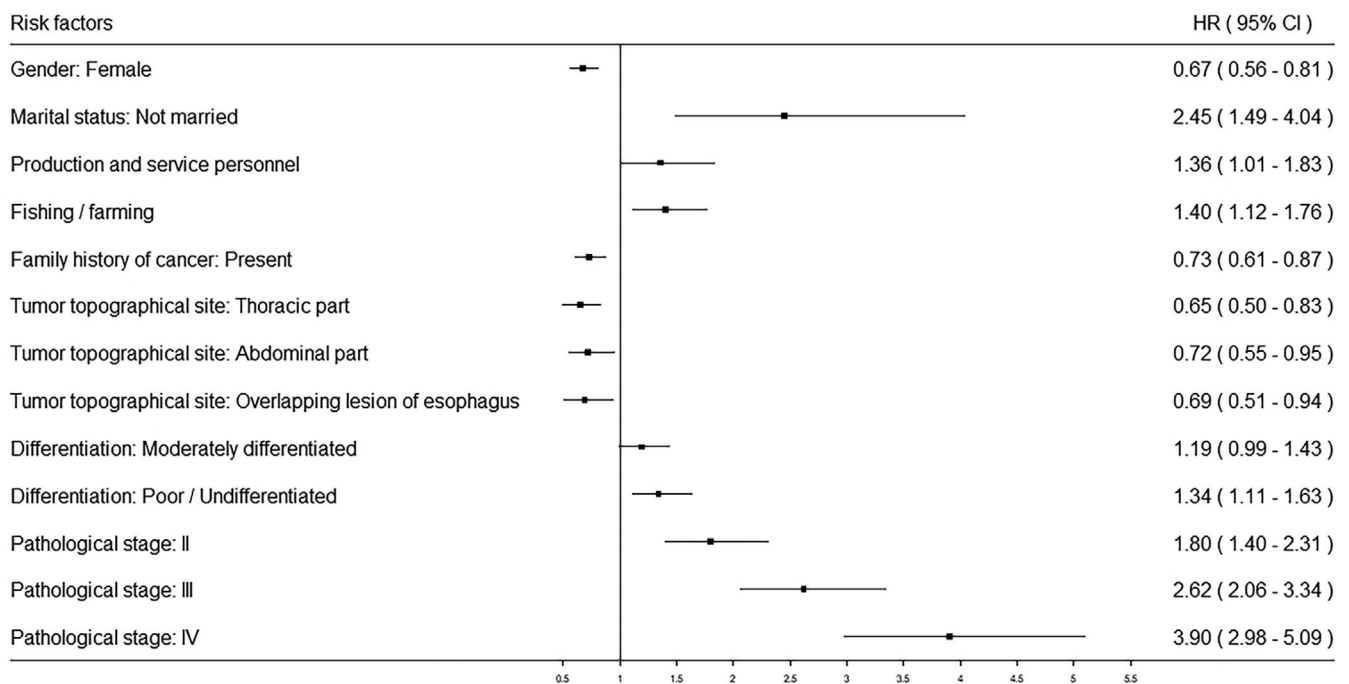


FIGURE 2 Forest plot of the significant risk factors related to the overall survival of esophageal cancer patients

FHC, $P < 0.001$) were independent protective factors affecting the prognosis of EC (Table 3 and Figure 2).

4 | DISCUSSION

This was a large multicenter study comprising of 5283 patients across several provinces in China. The latest population-based study in China in 2009-2011 showed that the age-standardized 5-year EC survival rate was 30.3%, and the 5-year EC net survival of the population of the United States in 2010-2014 was 20.0% [17-19]. Findings

from the present study showed that the 5-year OS rate was 39.07% in the investigated 18 hospitals and we found that gender, marital status, occupation, family history of any cancer, tumor topographical site, differentiation status, and pathological stage were associated with the survival rate of EC.

In our study, not married status was a negative prognostic factor for EC survival, with an HR of 2.45 (95% CI = 1.49-4.04). This result was consistent with previous studies. Du et al [20] identified that marital status was related to the survival of EC patients in the U.S. In their study, single (HR = 1.14, 95%CI = 1.11-1.17), divorced (HR = 1.16, 95%

CI = 1.13-1.19), and widowed (HR = 1.22, 95%CI = 1.19-1.26) patients had a higher risk of death compared to married patients. Zhang et al [21] showed that unmarried patients had poorer OS than married patients (HR = 1.22). The reasons why the single status affected the survival of EC patients may be related to their mental state, income, spiritual support. Subsequently, unmarried patients may have less financial and psychological support during their treatment than married patients.

Previous studies were mainly focused on the relationship between EC survival and occupation with harmful chemical substances exposure [22, 23]. Clin et al [24] performed a 10-year follow-up of 14,515 male workers to determine the correlation between occupational asbestos exposure and EC mortality. Their results indicated that the HR for asbestos exposure was 1.40. Our study suggested that the survival of patients who worked as the production and service personnel and farming/fishing was worse than that of patients who were enterprise personnel. This may be due to their low level of awareness of cancer prevention and control. Patients in farming/fishing could be more likely diagnosed with advanced-stage disease, leading to poor survival from EC.

Studies found that smoking was related to the survival of patients with various cancers, including prostate [25], lung [26], oral, and pharyngeal cancer [27]. Researchers also found that smoking was a poor prognosis factor of EC survival. In a prospective study including 411 EAC cases, patients in the highest smoking pack-year group had a poor prognosis (HR = 2.29) [28]. In a recent study, Spreafico et al [29] explored the negative effect of smoking on EAC survival (HR = 1.22). As the number of smoking pack-years increased, the risk of death increased. Similar results were also found in our study that the 5-year OS rate of smokers (HR = 1.13) was 37.84%, which was lower than that of never smokers (never smoker vs smoker: $P = 0.001$).

Alcohol consumption has been proved to be related to many diseases, including cancer [30-32]. Some studies have investigated the effect of alcohol consumption on EC survival [33, 34]. For instance, compared with ESCC patients who were life-long non-drinkers, the HRs of those who consumed 7-20 drinks/week or ≥ 21 drinks/week were 2.21 (95% CI = 1.27-3.84) or 2.08 (95% CI = 1.18-3.69) [12]. Huang et al [13] conducted a cohort study to evaluate the effect of alcohol consumption on EC. Their results indicated that the HR for the OS of drinkers was 1.22 (95% CI = 1.06-1.41) and the HR for disease-free survival (DFS) in drinkers was 1.16 (95% CI = 1.01-1.34). In our study, the median survival time of drinkers was 27.00 months, which was shorter than that of never drinkers (29.00 months) (never drinker vs drinker: $P = 0.596$).

BMI is a reliable indicator of the nutritional and metabolic status of a population and a sensitive prognostic

index for EC patients [35, 36]. However, the associations between BMI and the survival of patients with EC have been inconsistent. Our study suggested that the 5-year OS rates of patients with high and normal BMI were higher than those of patients with low BMI ($P = 0.014$). Deng et al [36] conducted a propensity score-matched (PSM) study to investigate whether a high BMI had any impact on the long-term survival of 132 EC patients who were treated with curative esophagectomy. Cox multivariate analysis showed that there was no significant difference between patients with a high BMI and those with a normal BMI. The same results were also observed in other studies. Takemoto et al [37] and Hasegawa et al [38] both suggested that BMI might not be a risk factor for EC survival. In addition, there were studies suggesting that the effect of BMI on EC survival was related to smoking status [39, 29]. For example, Sun et al [39] indicated that patients with low BMI (< 18.5) had a 2.22 times higher risk of EC-related death than patients with a high BMI (≥ 18.5) among never smokers. However, Yoon et al [40] conducted a study in EAC patients to investigate the impact of BMI by stratifying the patients according to smoking status. The HRs for disease-specific survival (DSS), DFS, and OS were 2.11, 2.03, and 1.97, respectively, in the obese group when compared with the normal weight group among never smokers. In different smoking status, the prognostic impacts of obesity and low BMI on ESCC survival varied, but could not be eliminated.

There is little information available about the relationship between blood type and EC survival. In this present multicenter study, univariate analysis results indicated that the HRs for B and O blood types were both 1.13. However, the ABO blood type was not significantly associated with survival in multivariate analysis. In recent years, the results of studies focused on the role of blood type in the survival of EC were inconsistent. Wang et al [15] demonstrated that ABO blood type was not related to survival among EC patients who underwent esophagectomy. Shiratori et al [41] demonstrated that the 5-year OS rate of patients with non-B blood type was 30.2%, which was lower than that of patients with type B blood (58.8%) among 181 Japanese ESCC patients. The 5-year OS rates of patients with blood types A, B, O, and AB were 50.0%, 45.4%, 50.8%, and 60.7%, respectively, in the study by Sun et al [42].

There was an interesting result observed in patients with FHC in our study. In the smoking and drinking subgroups, univariate and multivariate analyses demonstrated that patients with FHC had better OS than patients without FHC. Previous studies have shown that patients with FHEC have a poor prognosis. For example, Gao et al [43] conducted a study consisting of 600 ESCC hospital-based patients in Shanxi, China, and their results suggested that an increased risk of ESCC was related to FHC (OR = 1.72).

In another hospital-based cohort study by Yuequan et al [44], the 3-year OS rate and 5-year OS rate of patients with FHEC were 38.6% and 22.9%, respectively. FHEC was an independent risk factor in their multivariate analysis. Ghadimi et al [45] used a gamma frailty model to analyze the effect of FHC in 359 EC patients. Their results also indicated that FHC was a significant risk predictor for the survival of patients with EC. The 3- and 5-year OS rates of patients with FHC were 56.34% and 46.36%, respectively, in our study, which were higher than those of patients without FHC and conflicted with the results of previous studies. The results of subgroup analyses showed that the distributions of differentiation status and TNM stage were different between patients with and without FHC or FHEC. The proportion of patients with poor differentiation/undifferentiated histological status with FHC was 23.39%, which was lower than that of patients without FHC. The proportion of patients with stage I and II and with FHC was 44.22%, which was higher than that of patients without FHC (40.07%). The same results were observed in the group of patients with FHEC. This might be because patients with FHC were defined as a high-risk population and prior to be included in the cancer screening. Nevertheless, the specific effect of FHC on the survival of EC patients' needs further investigation.

One limitation of this study is that different diagnostic assessments and treatment levels in the various hospitals might have influenced the results. In future studies, we will investigate more cases in municipal and county hospitals. A second limitation is that smoking status, drinking status, and other variables were self-reported and recorded in the medical records. Hence, never-smokers may have been misclassified, especially in participants who were ex-smokers and had stopped smoking fewer than 15 years before. The proportion of the missing data of some variables, such as differentiation status was relatively high. However, it was within a reasonable range. The analysis of treatment methods was classified as surgery only, radiotherapy only, and chemotherapy only. We will analyze the detailed effects of treatment on EC survival in future studies. Further data are required to confirm these findings and to increase the precision of the effect for these exposures.

As conclusion, gender, marital status, occupation, family history of any cancer, tumor topographical site, differentiation status, and pathological stage were independent risk factors for EC survival in China. We expect that the findings could act as a guidance for enhancing the awareness of EC prevention and to change unhealthy lifestyles; and could assist authorities seeking to develop better surveillance strategies to increase the survival and quality of life of EC patients.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

DECLARATIONS

AUTHORSHIP

WQC and YTH designed the research. YTH, TTG, DL, YYL, and BES were contributors in writing the manuscript. TTG, LBD, XBS, NW, KRW, and MZ collected the data. YTH, TTG, and DL performed data analyses. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no potential conflicts of interest.

FUNDING

This study was funded by the National Key Research and Development Program of China (2018YFC1313100) and a grant from the National Natural Scientific Foundation of China (81871922).

ACKNOWLEDGMENTS

We gratefully thank the following hospitals for their cooperation with regard to providing, sorting, and verifying the cancer data: the Fourth Hospital of Hebei Medical University, the First Hospital of Shijiazhuang, Cixian Cancer Hospital, the Beijing Cancer Hospital, Cancer Hospital of the Chinese Academy of Medical Sciences, the First People's Hospital of Dongcheng, Henan Cancer Hospital, the People's Hospital of Jiyuan, the Third People's Hospital of Luoyang, Dongfang Hospital of Luoyang, Zhejiang Cancer Hospital, Haining Traditional Chinese Medicine Hospital, Zhejiang Jinhua Guangfu Hospital, Hubei Cancer Hospital, the First Hospital of Danjiangkou, the First People's Hospital of Xiangyang, the People's Hospital of Xiaolan, and the People's Hospital of Zhongshan

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: He Y, Liang D, Du L, et al. Clinical characteristics and survival of 5283 esophageal cancer patients: a multicenter study from eighteen hospitals across six regions in China. *Cancer Commun*. 2020;40:531–544. <https://doi.org/10.1002/cac2.12087>