Original Article

Comparison of prognostic factors of esophageal cancer between a Chinese cohort and the Surveillance, Epidemiology, and End Results (SEER) database: a retrospective cohort study

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Background: Esophageal cancer is a highly aggressive, early metastasis gastrointestinal malignancy, with geographic differences in prognosis. It is unknown whether there are differences in the survival in different regions among esophageal cancer patients who underwent the treatments. This study was to explore the influencing factors of esophageal cancer survival in patients from China and the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: The retrospective cohort study were conducted with 605 Chinese esophageal cancer patients in the Wuxi People's Hospital and 2,351 patients from the SEER database. The demographic and clinical data were collected from the two cohort, respectively. The outcome was the death during the follow-up. The follow-up ended on November 30, 2021. The Cox proportional hazards model was used in the univariate and multivariate survival analyses, with hazard ratio (HR) and 95% confidence interval (CI).

Results: In group one, the following were identified as the prognostic factors: female gender (HR =0.568; 95% CI: 0.398–0.811), T3 and T4 stages (HR =3.312; 95% CI: 2.493–4.401), N2 and N3 stages (HR =3.562; 95% CI: 2.631–4.824), and other subtypes of cancer (HR =0.393; 95% CI: 0.223–0.693). The following prognostic were factors identified in group two: age ≥65 years (HR =1.16; 95% CI: 1.058–1.276), female gender (HR =0.843; 95% CI: 0.752–0.945), T3 and T4 stages (HR =1.523; 95% CI: 1.373–1.690), M1 stage (HR =2.554; 95% CI: 2.303–2.832), treatment with surgery and chemotherapy (HR =0.507; 95% CI: 0.457–0.562), and other subtypes of cancer (HR =1.432; 95% CI: 1.298–1.581).

Conclusions: There may be some differences in prognostic factors between Chinese and American patients with esophageal cancer. It is indicated that different management strategies of esophageal cancer should be considered in different populations to improve the prognosis of patients.

Keywords: Esophageal cancer; prognostic factors; China; Surveillance, Epidemiology, and End Results (SEER); comparison

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Introduction

Esophageal cancer is the seventh most common cancer and the sixth leading killer of types of cancer in the world (1,2). It is a highly aggressive gastrointestinal malignancy with early metastasis and a poor prognosis, and the overall survival ranges from 15% to 25% worldwide (3). Esophageal cancer has two major histologic subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). The survival rate of both types is extremely poor because most cases are diagnosed at a late stage (4). In view of this, research that identifies the prognostic factors for esophageal cancer is necessary to improve the prognosis and survival rate of patients.

Many factors are associated with the survival of patients with esophageal cancer, such as age, gender, treatment methods, the tumor, and node, metastasis (TNM) staging system (5-11). Previous studies have shown that differences in the incidence and prognosis may be due to differences in ethnicities, lifestyles, socioeconomic status, therapeutic schedules and patients' options, as well as health care systems (12-14). Lin *et al.* reported the clinicopathological and survival of Chinese and Caucasian esophageal cancer patients who have been residing in the United States of America (USA) (15). This suggests that factors that affect prognosis may vary in patients with esophageal cancer from different populations (15). Xiao *et al.* assessed different treatment strategies for primary small cell carcinoma of the esophagus between Chinese and USA patients (16). However, these studies had relatively small sample sizes, or did not focus on the distribution and prognosis of different subtypes of esophageal cancer.

Herein, we investigated the demographic and clinical data of patients with esophageal cancer from a Chinese cohort and from the USA cohort based on the Surveillance, Epidemiology, and End Results (SEER) database. This study explored the prognostic factors of esophageal cancer and compared the differences between the two populations. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-145/rc).

Methods

Study design and population

In this retrospective cohort study, Chinese esophageal cancer patients in the Wuxi People's Hospital from January 2015 to April 2020 were selected. The inclusion criteria were as follows: (I) age ≥18 years, (II) patients who was diagnosed with primary esophageal cancer, and (III) patients who underwent surgery. All diagnoses of esophageal cancer were confirmed by morphologic examination, and the diagnosis codes were C15.900, C15.901, C15.801, C15.802, C15.100, and C15.100x003. A total of 605 patients were enrolled, and 66 patients were excluded because they were lost to follow-up. Then 539 patients were finally included in group one. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Wuxi People's Hospital (No. KY21038). Individual consent for this retrospective analysis was waived.

Patients with primary esophageal cancer between 2011 and 2016 in the USA were selected from the Incidence and Survival Statistics from SEER 18 Custom Data (with Additional Treatment Fields) (1975–2016 Varying). The SEER database is a population-based cancer registry covering 28% of the population of the USA and is a useful resource for cancer research. The site-specific histology and behavior codes were (C15.9-Esophagus, NOS), (C15.8-Overlapping lesion of the esophagus), and (C15.1-Thoracic esophagus). Finally, 2,351 patients were identified and included in group two.

Potential clinical factors

Data analyzed in this study were retrospectively retrieved from the electronic medical records of Wuxi People's Hospital and the SEER database, respectively. For comparison between groups, the demographic and clinical data collected were age, gender (male, female), tumor TNM stage (T1 + T2, T3 + T4; N0 + N1, N2 + N3; M0, M1), treatment methods (surgery only, surgery combined with chemotherapy), cancer subtypes (squamous cell, other cell), vital status (alive, dead), and follow-up time. The tumors were staged according to the seventh edition of the TNM classification of esophageal carcinoma by the American Joint Committee on Cancer.

Study outcome and follow-up

The outcome of this study was the death during the follow-up. The follow-up ended on November 30, 2021. In Chinses cohort, the median follow-up time was 22.00 (13.00, 37.00) months. In the SEER database, the median follow-up time was 9.00 (3.00, 22.00) months. The follow-up was terminated when the patient died during the follow-

up period.

Statistical analysis

In the baseline analysis, measurement data were analyzed with the Shapiro-Wilk test. Normally distributed data were expressed as mean ± standard deviation (mean ± SD), and data in a non-normal distribution were expressed as median and interquartile range M (Q1, Q3). Enumeration data were expressed as the number of cases and constituent ratio N (%), and comparison between groups was performed using the Chi-square test and the Fisher's exact test.

The Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) in the univariate and multivariate survival analyses. All variables were included in the multivariate analysis for comparison between the two populations. Then the influencing factors of the survival of esophageal cancer patients were further accessed in different gender. The overall survival rate was calculated using the Log-rank test. Forest plots were drawn according to the multivariate Cox analysis using R 4.02 software (https://www.r-project.org/). The two-sided test was used in all statistical analyses, and two-sided P<0.05 was considered statistically significant. Cox regression analysis was conducted using SPSS 20.0 (IBM, SPSS Inc., Chicago, IL, USA).

Results

Patient description

The characteristics of esophageal cancer patients in the two groups were shown in *Table 1*. A total of 605 patients were enrolled, and 66 patients were excluded because they were lost to follow-up. Then 539 patients were finally included in group one. Of which, 436 (80.89%) patients were males, and 103 (19.11%) were females. Among them, 280 (51.95%) patients were <65 years old, and 259 (48.05%) patients were ≥65 years old. The median follow-up time was 22.00 (13.00, 37.00) months. In terms of morphological characteristics of cancer cells, 519 (96.29%) were diagnosed with ESCC, and 20 (3.71%) were diagnosed with other subtypes of cancer (such as EAC and small cell carcinoma). At the end of follow-up, 273 patients (50.65%) were alive, and 266 patients (49.35%) had died. In group two, 1,801 (76.61%) patients were males, and 550 (23.39%) were females. Among them, 1,077 (45.81%) patients were <65 years old, and 1,274 (54.19%) patients were ≥65 years old. The median follow-up time was 9.00 (3.00, 22.00) months. A total of 953 (40.54%) were diagnosed with ESCC, and 1,398 (59.46%) were diagnosed with other subtypes of cancer (such as EAC and small cell carcinoma). At the end of follow-up, 543 patients (23.10%) were alive, and 1,808 patients (76.90%) had died. There were statistical differences in age (χ^2=6.632), gender (χ^2=4.603), stage (χ^2=184.270), treatment (χ^2=35.556), cancer cell classification (χ^2=545.380), vital status (χ^2=164.275) and median follow-up time (Z=8.541) between the two groups, with all P<0.001. A flow diagram of the two groups was displayed in *Figure 1*.

Subgroup analyses

Overall survival rate

We analyzed the overall survival rates of the two groups. As shown in *Table 2*, the results suggested that, in group one, the overall survival rates significantly differed based on gender (χ^2=11.399; P=0.001), T stage (χ^2=89.849; P<0.001), N stage (χ^2=103.260; P<0.001), treatment method (χ^2=7.788; P=0.005), and cancer cell classification (χ^2=7.608; P=0.006) (*Figure 2*). In group two, the overall survival rates were significantly differed based on age (χ^2=4.427; P=0.035), TNM stage (T stage: χ^2=47.202; P<0.001. N stage: χ^2=7.142; P=0.008. M stage: χ^2=313.502; P<0.001), treatment method (χ^2=52.697; P<0.001), and cancer cell classification (χ^2=30.582; P<0.001) (*Figure 3*).

Gender

In the subgroup analysis by gender, gender differences in the two groups were analyzed. In group one, males had a significantly older age (χ^2=13.101; P<0.001) than females. The proportions of patients who only received surgery (χ^2=3.872; P=0.049) and who were alive (χ^2=10.562; P=0.001) during the follow-up period were significantly higher in males than females. Furthermore, the follow-up time (Z=2.689; P<0.001) was significantly shorter in males than females. In group two, the proportions of patients who were at M stage (χ^2=373.110; P<0.001), who only received surgery (χ^2=4.166; P=0.041), and who were diagnosed with ESCC (χ^2=121.433; P<0.001) were significantly higher in males than females. Also, the follow-up time (Z=8.898; P<0.001) was significantly shorter in males than females (*Table 3*).

Influencing factors of the survival of patients with esophageal cancer in two groups

According to the univariate Cox regression analysis, female gender (HR =0.554, 95% CI: 0.390–0.787), T3 and T4

Table 1 Baseline characteristics of esophageal cancer patients in the two groups

Variables	Group one (n=539)	Group two (n=2,351)	χ^2/Z	P
Age, years, n (%)			6.632	0.010
<65	280 (51.95)	1,077 (45.81)		
≥65	259 (48.05)	1,274 (54.19)		
Gender, n (%)			4.603	0.032
Male	436 (80.89)	1,801 (76.61)		
Female	103 (19.11)	550 (23.39)		
T Stage, n (%)			1.202	0.273
T1 + T2	242 (44.90)	1,117 (47.51)		
T3 + T4	297 (55.10)	1,234 (52.49)		
N Stage, n (%)			0.542	0.461
N0 + N1	456 (84.60)	2,018 (85.84)		
N2 +N3	83 (15.40)	333 (14.16)		
M Stage, n (%)			184.270	<0.001
M0	533 (98.89)	1,679 (71.42)		
M1	6 (1.11)	672 (28.58)		
Treatment, n (%)			35.556	<0.001
Surgery only	304 (56.40)	993 (42.24)		
Surgery + chemotherapy	235 (43.60)	1,358 (57.76)		
Cancer cell classification, n (%)			545.380	<0.001
Squamous cell	519 (96.29)	953 (40.54)		
Other cell	20 (3.71)	1,398 (59.46)		
Vital status, n (%)			164.275	<0.001
Alive	273 (50.65)	543 (23.10)		
Dead	266 (49.35)	1,808 (76.90)		
Follow-up, months, M (Q_1, Q_3)	22.00 (13.00, 37.00)	9.00 (3.00, 22.00)	8.541	<0.001

stages (HR =3.474; 95% CI: 2.635–4.580), N2 and N3 stages (HR =4.025; 95% CI: 3.044–5.394), treatment with surgery and chemotherapy (HR =1.402; 95% CI: 1.102–1.784), and other subtypes of cancer (such as EAC and small cell carcinoma) (HR =0.466; 95% CI: 0.265–0.817) were the potential prognostic factors of esophageal cancer in group one. In group two, age ≥65 years old (HR =1.102; 95% CI: 1.004–1.209), T3 and T4 stages (HR =1.373; 95% CI: 1.251–1.508), N2 and N3 stages (HR =1.187; 95% CI: 1.043–1.351), M1 stage (HR =2.334; 95% CI: 2.112–2.578), treatment with surgery and chemotherapy (HR =0.714; 95% CI: 0.650–0.785), and other subtypes of cancer (HR =1.291; 95% CI: 1.176–1.417) were the potential prognostic factors (*Table 4*).

All variables were then included in the multivariate Cox regression for further analysis. As shown in *Table 5*, the results suggested that, in group one, female gender (HR =0.568; 95% CI: 0.398–0.811), T3 and T4 stages (HR =3.312; 95% CI: 2.493–4.401), N2 and N3 stages (HR =3.562; 95% CI: 2.631–4.824), and other subtypes of cancer (such as EAC and small cell carcinoma) (HR =0.393; 95% CI: 0.223–0.693) were identified as the prognostic factors of esophageal cancer (*Figure 4*). The prognostic factors identified in group two were age ≥65 years (HR =1.162;

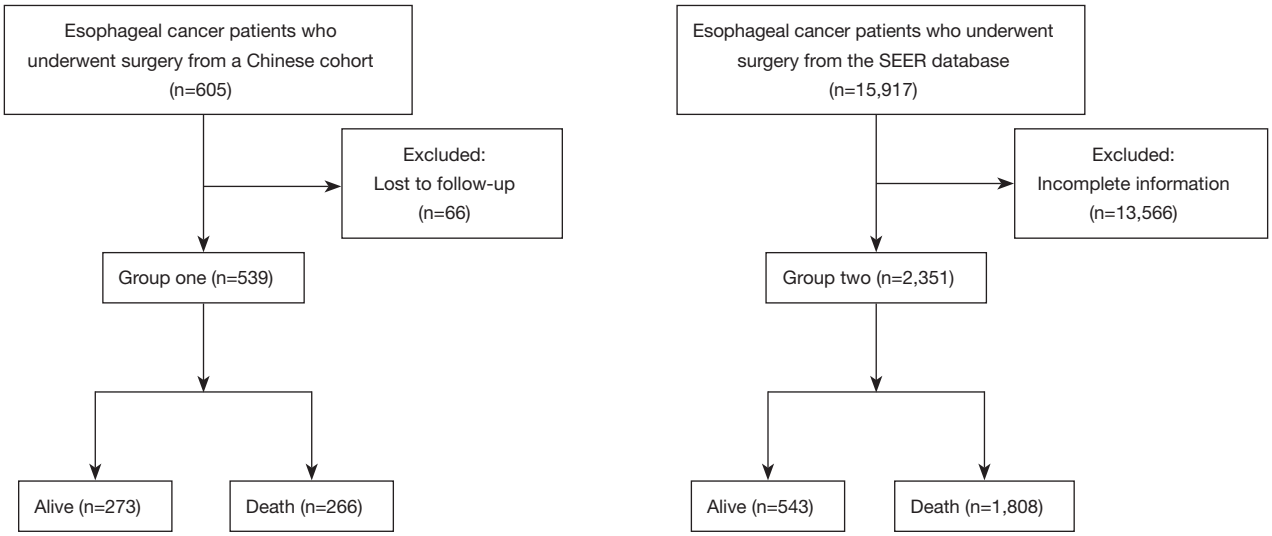

Figure 1 The flow diagram of sample selection in the two groups.

Table 2 The overall survival in the two groups

Variables	Group one (n=273)				Group two (n=543)			
	No.	OS (%)	Log-rank	P	No.	OS (%)	Log-rank	P
Age, years, n (%)			0.120	0.729			4.427	0.035
<65	140 (51.28)	25.97			274 (50.46)	11.65		
≥65	133 (48.72)	24.68			269 (49.54)	11.44		
Gender, n (%)			11.399	0.001			0.835	0.361
Male	206 (75.46)	38.22			406 (74.77)	17.27		
Female	67 (24.54)	12.43			137 (25.23)	5.83		
T stage, n (%)			89.849	<0.001			47.202	<0.001
T1 + T2	173 (63.37)	32.10			322 (59.30)	13.70		
T3 + T4	100 (36.63)	18.55			221 (40.70)	9.40		
N stage, n (%)			103.260	<0.001			7.142	0.008
N0 + N1	255 (93.41)	47.31			481 (88.58)	20.46		
N2 + N3	18 (6.59)	3.34			62 (11.42)	2.64		
M stage, n (%)			2.534	0.111			313.502	<0.001
M0	272 (99.63)	50.46			495 (91.16)	21.05		
M1	1 (0.37)	0.19			48 (8.84)	2.04		
Treatment, n (%)			7.788	0.005			52.697	<0.001
Surgery only	169 (61.90)	31.35			223 (41.07)	9.49		
Surgery + chemotherapy	104 (38.10)	19.29			320 (58.93)	13.61		
Cancer cell classification, n (%)			7.608	0.006			30.582	<0.001
Squamous cell	266 (97.44)	49.35			180 (33.15)	7.66		
Other cell	7 (2.56)	1.30			363 (66.85)	15.44		
Follow-up, months, M (Q_1, Q_3)	30.00 (18.00, 45.00)				33.00 (20.00, 52.00)			

OS, overall survival.

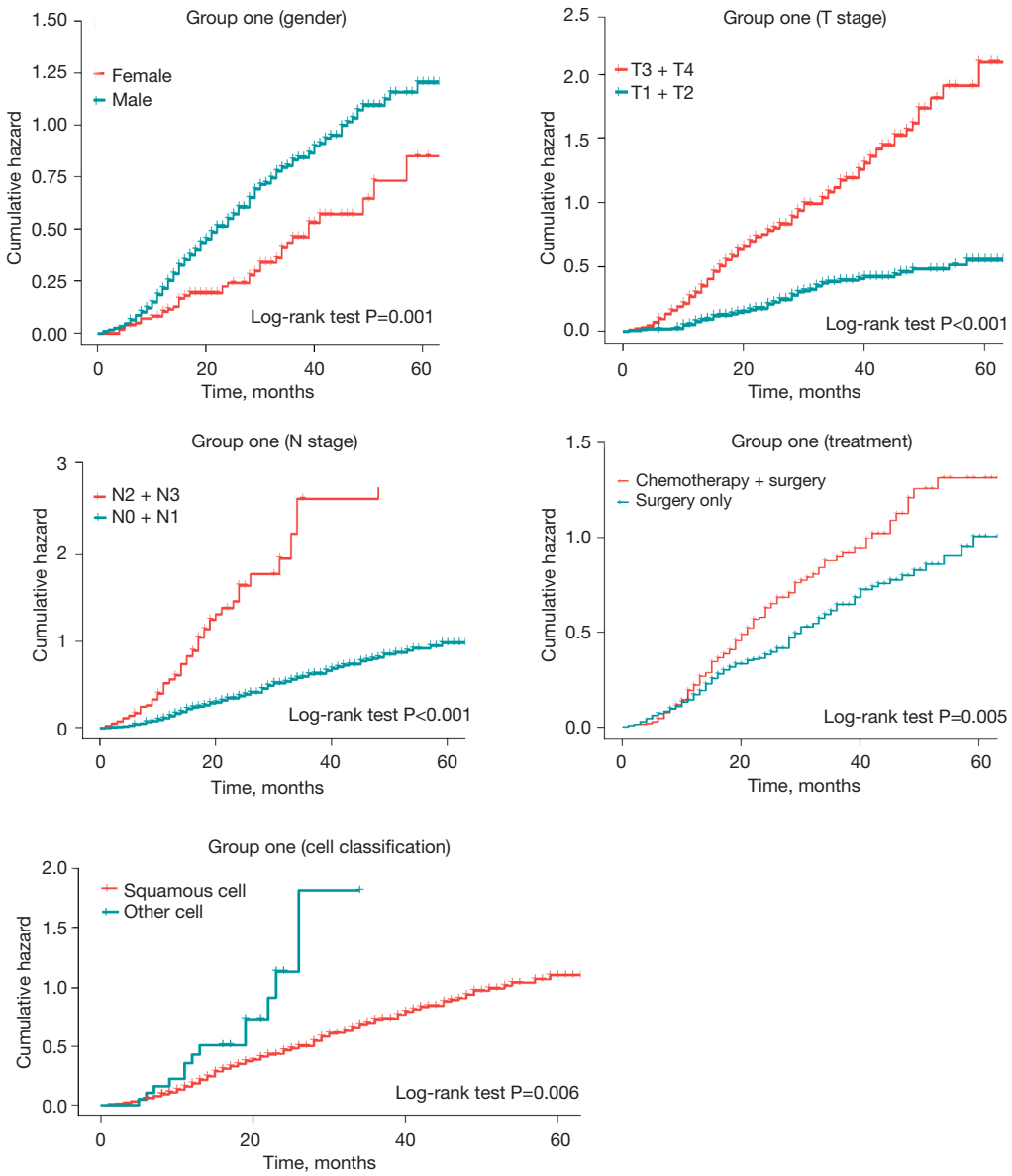

Figure 2 Cumulative incidence of overall survival in group one.

95% CI: 1.058–1.276), female gender (HR =0.843; 95% CI: 0.752–0.945), T3 and T4 stages (HR =1.523; 95% CI: 1.373–1.690), M1 stage (HR =2.554; 95% CI: 2.303–2.832), treatment with surgery and chemotherapy (HR =0.507; 95% CI: 0.457–0.562), and other subtypes of cancer (HR =1.432; 95% CI: 1.298–1.581) (*Figure 5*).

Discussion

Esophageal cancer is a very common cancer worldwide with high morbidity. However, little attention has been paid to the differences in the prognostic factors among different populations. In the present study, notable differences were found in demographics, tumor stages, treatment methods, and cancer subtypes of esophageal cancer in Chinese and American patients. By subgroup analysis, the overall survival of Chinese patients was higher than that in the American population. Gender and T stage were independently associated with cancer survival in both groups. Age ≥65 years old, M1 stage, and treatment with surgery and chemotherapy were identified as prognostic factors of the survival in American patients, while these variables were not

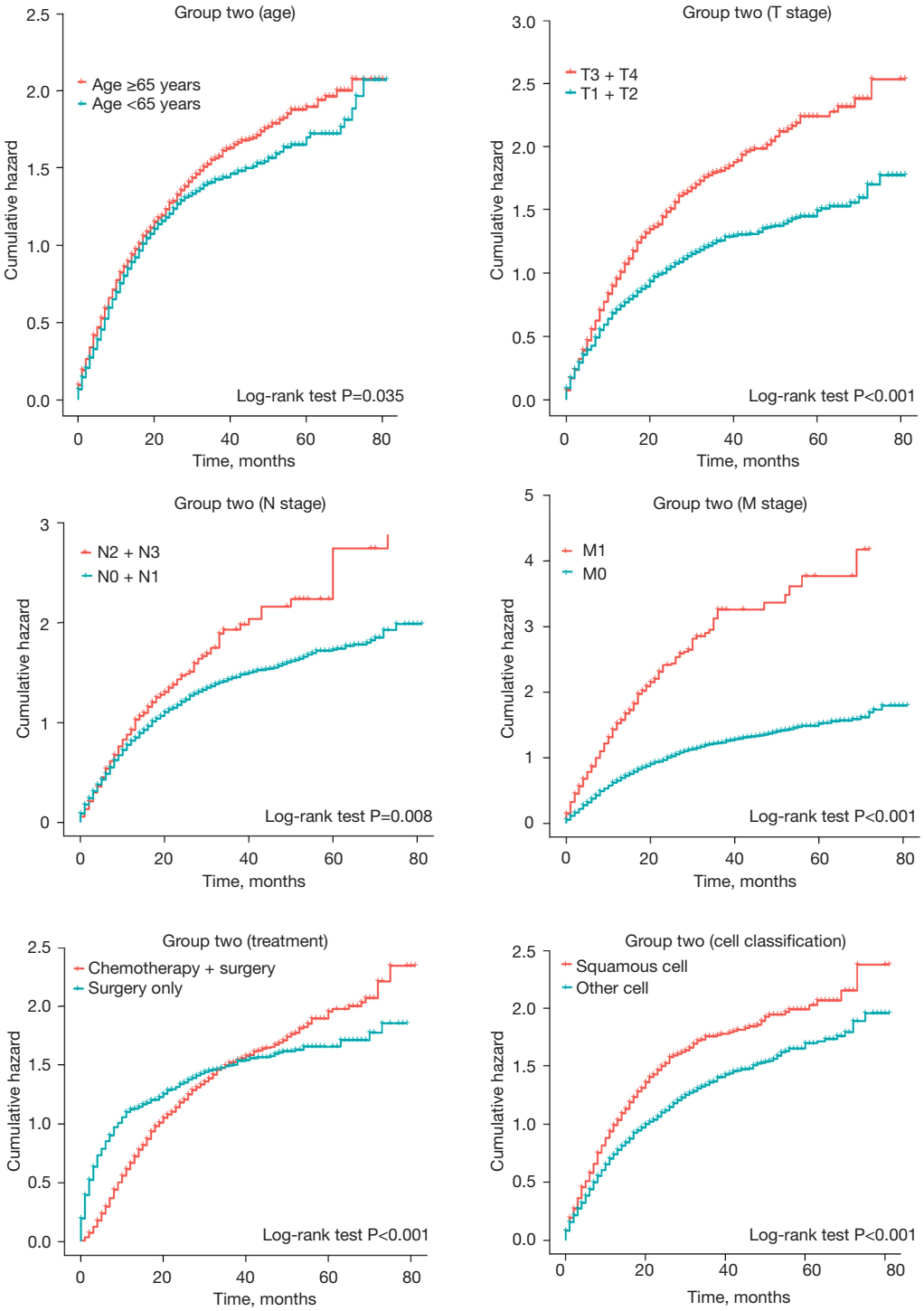

Figure 3 Cumulative incidence of overall survival in group two.

Table 3 Subgroup analysis by gender in two groups

Variables	Group one (n=539)				Group two (n=2,351)			
	Male (n=436)	Female (n=103)	χ^2/Z	P	Male (n=1,801)	Female (n=550)	χ^2/Z	P
Age, n (%)			13.101	<0.001			3.436	0.064
<65 years	243 (55.93)	37 (35.92)			844 (46.86)	233 (42.36)		
≥65 years	193 (44.27)	66 (64.08)			957 (53.14)	317 (57.64)		
T stage, n (%)			2.918	0.088			0.105	0.746
T1 + T2	188 (43.12)	54 (52.43)			859 (47.70)	258 (46.91)		
T3 + T4	248 (56.88)	49 (47.57)			942 (52.30)	292 (53.09)		
N stage, n (%)			0.754	0.385			3.250	0.071
N0 + N1	366 (83.94)	90 (87.38)			1,533 (85.12)	485 (88.18)		
N2 +N3	70 (16.06)	13 (12.62)			268 (14.88)	65 (11.82)		
M stage, n (%)			0.023	0.878			373.110	<0.001
M0	431 (98.85)	102 (99.03)			542 (30.09)	420 (76.36)		
M1	5 (1.15)	1 (0.97)			1,259 (69.91)	130 (23.64)		
Treatment, n (%)			3.872	0.049			4.166	0.041
Surgery only	237 (54.36)	67 (65.05)			740 (41.09)	253 (46.00)		
Surgery + chemotherapy	199 (45.64)	36 (34.95)			1,061 (58.91)	297 (54.00)		
Cancer cell classification, n (%)			0.227	0.634			121.433	<0.001
Squamous cell	419 (96.10)	100 (97.09)			619 (34.37)	334 (60.73)		
Other cell	17 (3.90)	3 (2.91)			1,182 (65.63)	216 (39.27)		
Vital status, n (%)			10.562	0.001			1.328	0.249
Alive	206 (47.25)	67 (65.05)			406 (22.54)	137 (24.91)		
Dead	230 (52.75)	36 (34.95)			1,395 (77.46)	413 (75.09)		
Follow-up, months, M (Q_1, Q_3)	21.00 (13.00, 35.00)	29.00 (15.00, 40.00)	2.689	<0.001	9.00 (3.00, 22.00)	10.00 (3.00, 23.00)	8.898	<0.001

statistically significant in Chinese patients.

Previous studies reported that, in China, esophageal cancer is a leading cause of high mortality, and ESCC is the most common subtype (17-19). However, the incidence of esophageal cancer is not high in the USA, where EAC is the most common subtype (20). Consistent with this, our results suggested a vast discrepancy in the distribution of cancer subtypes in the two populations. In our study, a decreased risk of death was found in Chinese patients with EAC compared to those with ESCC, while EAC was identified to be a risk factor in American patients. The discrepancy here may be due to differences in genetic and environmental factors between the Chinese and American populations (17,21,22). In view of this, clinicians should consider different therapeutic strategies for the management of patients with esophageal cancer in different populations.

Currently, controversies still exist in the treatment methods of esophageal cancer. In our study, differences were observed between the two groups depending on whether they had surgery only or surgery combined with chemotherapy. The efficacy of surgery combined with chemotherapy was significantly better than pure surgical treatment in American patients, while there was no remarkable difference between the two treatment methods

Table 4 Univariate Cox analysis for esophageal cancer patients in the two groups

Variables	Group one (n=539)			Group two (n=2,351)		
	HR	95% CI	P	HR	95% CI	P
Age						
<65 years	Ref			Ref		
≥65 years	0.959	0.754–1.220	0.732	1.102	1.004–1.209	0.041
Gender						
Male	Ref			Ref		
Female	0.554	0.390–0.787	0.001	0.951	0.853–1.062	0.374
T stage						
T1 + T2	Ref			Ref		
T3 + T4	3.474	2.635–4.580	<0.001	1.373	1.251–1.508	<0.001
N stage						
N0 + N1	Ref			Ref		
N2 + N3	4.025	3.044–5.394	<0.001	1.187	1.043–1.351	0.010
M stage						
M0	Ref			Ref		
M1	2.010	0.828–4.877	0.123	2.334	2.112–2.578	<0.001
Treatment						
Surgery only	Ref			Ref		
Surgery + chemotherapy	1.402	1.102–1.784	0.006	0.714	0.650–0.785	<0.001
Cancer cell classification						
Squamous cell	Ref			Ref		
Other cell	0.466	0.265–0.817	0.008	1.291	1.176–1.417	<0.001

HR, hazard ratio; CI, confidence interval.

in Chinese patients. Chemotherapy is an effective adjuvant therapy for esophageal cancer (23). It can help kill cancer cells, shrink the tumor, control the cancer development, and even reduce the recurrence rate after treatment (24). Similarly, A randomized controlled study based on patients in the United Kingdom showed that the median overall survival was significantly higher in the chemotherapy group as compared with the surgery alone group (25). In the study of Xiao *et al.* (16), chemotherapy improved the overall survival in both Chinese and American groups. They also reported that chemotherapy failed to improve survival in localized stage patients. This may explain why no significant differences were found in Chinese patients in our study. There were only 6 (1.11%) Chinese patients at the M1 stage, while 28.58% of American patients were at the same stage, which may contribute to the difference. In addition, the effects of preoperative and postoperative chemotherapy were inconsistent in patients of different populations (26,27). We may suggest that optimal chemotherapy drugs, doses, and regimens need to be further investigated for patients of different ethnic groups to achieve a high completion rate and improve the prognosis of esophageal cancer.

Our study has some limitations. First, some potential variables that may also affect the cancer prognosis were not included in our study because chemotherapy types, doses, and duration, as well as the use of other oral agents, were not recorded in the SEER database. Second, due to the single center and the small sample size, the Chinese patients enrolled in our study cannot represent all the Chinese population. Therefore, a multi-center prospective study

Table 5 Multivariate Cox analysis for esophageal cancer patients in the two groups

Variables	Group one (n=539)			Group two (n=2,351)		
	HR	95% CI	P	HR	95% CI	P
Age						
<65 years	Ref			Ref		
≥65 years	0.968	0.754–1.244	0.801	1.162	1.058–1.276	0.002
Gender						
Male	Ref			Ref		
Female	0.568	0.398–0.811	0.002	0.843	0.752–0.945	0.003
T stage						
T1 + T2	Ref			Ref		
T3 + T4	3.312	2.493–4.401	<0.001	1.523	1.373–1.690	<0.001
N stage						
N0 + N1	Ref			Ref		
N2 + N3	3.562	2.631–4.824	<0.001	1.061	0.927–1.214	0.388
M stage						
M0	Ref			Ref		
M1	0.948	0.384–2.340	0.907	2.554	2.303–2.832	<0.001
Treatment						
Surgery only	Ref			Ref		
Surgery + chemotherapy	0.961	0.744–1.241	0.760	0.507	0.457–0.562	<0.001
Cancer cell classification						
Squamous cell	Ref			Ref		
Other cell	0.393	0.223–0.693	0.001	1.432	1.298–1.581	<0.001

HR, hazard ratio; CI, confidence interval.

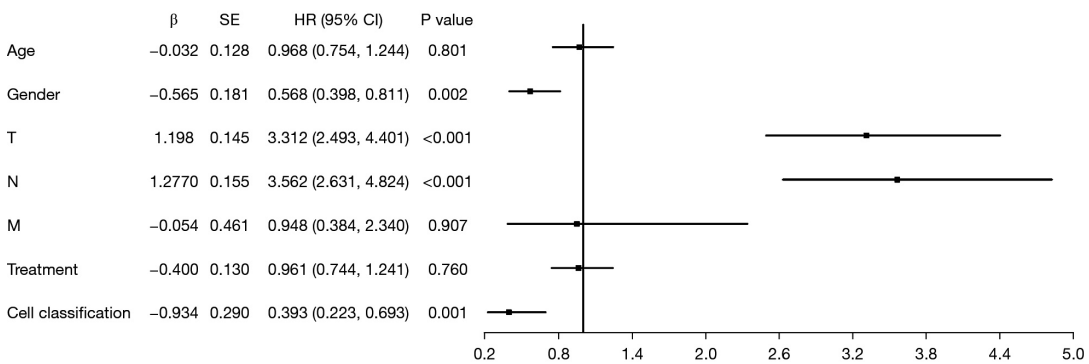

Figure 4 Forest plot for multivariate analysis of patients in group one. SE: standard error; HR: hazard ratio.

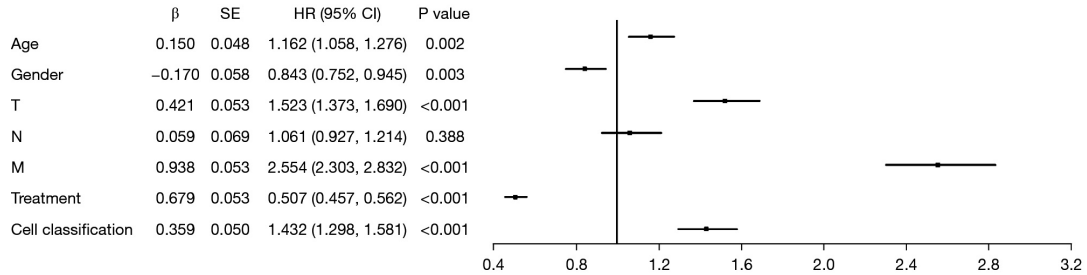

Figure 5 Forest plot for multivariate analysis of patients in group two. SE, standard error; HR, hazard ratio.

with large sample size is preferred for further investigation of differences among populations.

Conclusions

Notable differences were found in demographics, tumor stages, treatment methods, and cancer subtypes of esophageal cancer in Chinese and American patients. different management strategies of esophageal cancer should be considered in different populations to improve the prognosis of patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-145/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Wuxi People's Hospital (No. KY21038). Individual consent for this retrospective analysis was waived.

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