The impact of preoperative use of calcium channel blockers on outcomes of patients undergoing esophagectomy: a propensity score-matched cohort study

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Abstract

BACKGROUND

In this study, we compared the effects of using preoperative CCBs on perioperative outcomes, cancer recurrence and overall survival in patients undergoing esophagectomy.

METHODS

A retrospective cohort study was performed on patients who underwent esophagectomy at the Sun Yat-Sen University Cancer Center (n=2415, 2009-2013). Univariate and multivariate logistic regression analyses were performed to assess the perioperative outcomes, while recurrence-free survival and overall survival were assessed using Kaplan-Meier survival estimates and compared using a multivariate Cox proportional hazards regression, adjusted with propensity scores.

RESULTS

There were 162 patients in the CCB group and 1110 patients in the non-CCB group and the total incidence of perioperative complications was 45.7% in the CCB group and 42.5% in the non-CCB group. The differences in total perioperative complications and other perioperative outcomes were not significantly different between the two groups (P>0.05). The mortality rate was not significantly different between the two groups after matching (38.1% vs 31.6%, P=0.233). The difference in recurrence rate between the two groups was not statistically significant after matching (43.2% vs 32.9%, P = 0.061). Overall survival was shorter in patients with preoperative CCB use than in patients without CCB use (hazards ratio: 1.517, 95% confidence intervals (CI): 1.036-2.220, P=0.030). The multivariate Cox proportional hazards regression adjusted with propensity scores found that a history of smoking cigarettes, clinical stage III at diagnosis, preoperative CCB use, preoperative diuretics use, operation type and postoperative chemotherapy affected the overall survival of patients after esophagectomy. Recurrence-free survival was similar between the CCB and non-CCB groups (HR: 1.425, 95%CI: 0.989-2.053, P=0.054). A history of chronic lung disease, hypertension, and preoperative use of beta-blockers affected the recurrence-free survival of patients after esophagectomy.

CONCLUSION

Preoperative CCBs use was associated with shorter overall survival but did not affect recurrence-free survival or the postoperative complications for patients undergoing esophagectomy.

Background

Hypertension is a highly prevalent disease that affects approximately 30–45% of the general population (1) and antihypertensive medications are among the most commonly prescribed medications. The beneficial therapeutic effect of antihypertensive medications on controlling blood pressure has been well established in previous studies (2). Moreover, the association between antihypertensive medications and

the risk of cancer, such as breast cancer (3), renal cell carcinoma (4), and prostate cancer (5), has been a concern for nearly 50 years (6). Recently, the potential of antihypertensive medications to affect cancer progression has received increasing interest (7). Some epidemiological studies have shown that beta-blockers might be associated with longer survival and reduced mortality in patients with non-small-cell lung cancer, colorectal cancer, and prostate cancer (8–10). Esophageal cancer ranked fourth in cancer mortality in China, with an estimated 375,000 deaths from esophageal cancer in 2015(11). The prevalence of cardiovascular diseases is consistently higher in older adults (12), and esophageal cancer also affects elderly people more often; therefore, antihypertensive medications is commonly used to treat these comorbidities among esophageal cancer patients (13). However, study on esophageal cancer had never been considered. Thus, determining whether antihypertensive medications affect the prognoses of esophageal cancer patients is highly desirable.

Calcium channel blockers (CCBs) are one of the most commonly prescribed cardiovascular medications for patients with hypertension and coronary heart disease, accounting for more than 30% of antihypertensive medications used (14). Patients will continue to take such medications during oncology treatment, but the long-term safety of these medications has been questioned. Studies on the association between CCBs usage and cancer prognosis or risk remain controversial. CCBs may inhibit apoptosis to promote tumor cell proliferation, which is a theory that has been supported by several in vitro studies and animal studies (15–17). However, Jan et al. found that CCBs enhanced apoptosis of prostate cancer cells and might have a protective effect on prostate cancer (5). Some studies showed that CCB usage significantly increased cancer mortality (18, 19), while other studies did not find this relationship (14). To obtain further data on the possible influence of CCBs usage on cancer outcomes, we conducted an observational study with 2415 patients who underwent esophagectomy from 2009 to 2013 with data in the Sun Yet-Sen University Cancer Center Database.

Methods

We performed a retrospective cohort study involving patients with esophageal cancer (n = 2415) who underwent esophagectomy at the Sun Yat-Sen University Cancer Center from November 2009 to July 2013. The follow-up period ended in May 2017. The study was reviewed and approved by the Sun Yat-Sen University Cancer Center review board. The study protocol was granted exemption from written informed consent (not human subjects research) by the Sun Yat-Sen University Cancer Center review board.

Only the records of patients with esophageal cancer where esophagectomy was indicated were included in the analysis. Patients were excluded if the surgery was performed in other hospitals, if the operation was palliative, if the final diagnosis was a benign tumor, if tumor metastases were present, if neoadjuvant chemoradiation was provided, or if other systemic tumors existed. Of the original 2415 patients, 1272 patients met the inclusion criteria and were divided into 2 groups: used (CCB group, n = 162) or did not use (n = 1110) preoperative CCB (non-CCB group) (Fig. 1).

We collected follow-up data from the patients' medical records, hospital surgery database or pathology database (or both); after a letter of introduction was sent to the patients, telephone contact was established with the patients or their families. Independent investigators prospectively collected the data on each patient. We obtained the demographics, oncologic characteristics, and operative characteristics of all patients, including age, sex, preoperative medications, tumor site, pathological stage, clinical stage, transfusion, postoperative complications including cardio-cerebral events and infection from thoracotomy, and 30-day all-cause mortality.

The major outcomes included recurrence-free survival and overall survival. Recurrence was defined as radiologic evidence of local recurrence or distant metastatic disease. Recurrence-free survival was calculated from the date of the operation to the date of recurrence. For patients without a record of recurrence, recurrence-free survival was defined as the time between the date of the operation and the date of the last follow-up or the date of death. Overall survival was calculated from the date of the operation to the date of death from any cause.

Because this was an observational study, a propensity score-adjusted analysis was performed to control for selection bias as a result of nonrandom assignment to the 2 groups. Patients in the CCB and non-CCB groups were matched using the propensity-score matching method (20), which was carried out using R software version 2.12.1. The propensity score was calculated with consideration for all baseline variables except for history of hypertension, as shown in Table 3. We used the forward procedure, and variables were included up to a limit of a monotonized p-to-enter value of < 0.2. Then, we applied 1:1 nearest-neighbor matching without replacement to ensure that conditional bias was minimized. A caliper width of 0.001 resulted in the best trade-off between homogeneity and minimal loss of sample size. Small absolute values in standardized differences (< 25%) were assumed to support the assumption of balance between the treatment groups (20).

Table 3

Association of Preoperative CCB use With Postoperative outcomes in surgical patients

Surgical Characteristics	Use of CCB		Univariate OR	P	Adjusted OR	95%CI	P
	YES(n = 162)	NO(n = 1110)					
Perioperative-complication	74(45.7)	472(42.5)	1.137	0.449	0.808	0.268–2.433	0.704
MACE	3(1.9)	19(1.7)	1.083	0.898			0.998
Pneumonia	30(18.5)	218(19.6)	0.930	0.737	0.747	0.201–2.777	0.664
Infection in Thoracotomy	34(21.0)	166(15.0)	1.511	0.050	1.093	0.295–4.056	0.894
Anastomotic leakage	15(9.3)	111(10.0)	0.918	0.768	0.752	0.140–4.047	0.740
Anastomotic stenosis	6(3.7)	55(5.0)	0.738	0.488			0.998
Reoperation	6(3.7)	42(3.8)	0.978	0.960	0.316	0.041–2.437	0.316
ICU Visit	150(92.6)	999(90.0)	1.389	0.299	1.141	0.107–12.200	0.913
Readmission to ICU	6(3.7)	40(3.6)	1.029	0.949	0.316	0.041–2.437	0.269
Total ICU hours(h)	40.0 ± 89.6	39.7 ± 101.2		0.966			
Transfusion during surgery	16(9.9)	100(9.0)	1.107	0.720	0.886	0.177–4.432	0.883
Mortality in 30days	2(1.2)	20(1.8)	0.681	0.607			0.998
Hospital stay(d)	23.3 ± 13.2	25.0 ± 32.5		0.244			

Statistical analyses were carried out using IBM SPSS 19.0 (SPSS Inc., Chicago, IL). Continuous and categorical variables are reported as the mean ± SD or percentage and compared with 2-sample t-tests or $\chi 2$ tests (2-tailed), respectively. Missing data values for dichotomous variables were assigned the most frequent value, whereas continuous variables were assigned the median value, except for body surface area, which was assigned the sex-specific median value (21). Univariate and multivariate logistic regression analyses were performed to assess the associations among demographic, therapeutic and perioperative outcome variables. The results are reported as percentages and odds ratios (ORs) with 95%

confidence intervals (CIs). The univariable association between recurrence-free survival or overall survival and preoperative CCB use was assessed with Kaplan-Meier survival estimates, and the groups were compared with log-rank tests and with univariable Cox proportional hazards regression. Multivariate Cox proportional hazards regression analysis adjusting for propensity score was performed to assess the associations between preoperative CCB use and recurrence-free survival and overall survival. The results are reported as percentages and hazards ratios (HRs) with 95% CIs. All reported P values were 2-sided, and $P < 0.05$ was considered statistically significant.

Results

In total, 1272 patients who underwent esophagectomy were divided into two groups: those who used (n = 162, 12.7%) or did not use (n = 1110, 87.3%) preoperative CCBs (non-CCB users). The distribution of classes of preoperatively used CCBs is that nifedipine was the most commonly used active ingredient (61.7%), followed by amlodipine (19.1%), nimodipine (9.9%), felodipine (4.9%) and nitrendipine (4.3%). The comparisons of patient demographic and clinical data between the two groups are illustrated in Table 1. Most characteristics, oncologic and therapeutic variables were not significantly different between the two groups. However, the patients using CCBs preoperatively were older and had a more frequent history of chronic lung disease and hypertension than those who did not use CCBs preoperatively.

Table 1
Characteristics of CCB users and Non CCB users With Esophageal Cancer

N (%)	Use of CCB		P for Difference
	YES(n = 162)	NO(n = 1110)	
Age at diagnosis	63.4 ± 8.2	58.9 ± 9.1	< 0.001
Sex			
Male	129(79.6)	893(80.5)	0.806
Current Or Recent Cigarette Smoker	101(62.3)	711(64.1)	0.672
Current Or Recent Alcohol intake	53(32.7)	396(35.7)	0.462
BMI (kg/m2)	22.1 ± 3.2	21.7 ± 3.1	0.113
Clinical stage at diagnosis			
I	24(14.8)	143(12.9)	0.882
II	55(34.0)	410(36.9)	
III	83(51.2)	557(50.2)	
Primary cancer site			
upper segment	11(6.8)	102(9.2)	0.068
middle segment	99(61.1)	722(65.0)	
inferior segment	52(32.1)	286(25.8)	
Histological type			
squamous carcinoma	154(95.1)	1046(94.2)	0.670
Tumor Differentiation			
Poorly differentiated	65(40.1)	444(40.0)	0.793
moderately differentiated	78(48.1)	553(49.8)	
high differentiated	19(11.7)	113(10.2)	
Diabetes	18(11.1)	79(7.1)	0.074
Chronic Lung Dis	21(13.0)	256(23.1)	0.004
Cerebrovascular Dis	6(3.7)	31(2.8)	0.519
CHD	2(1.2)	15(1.4)	1.000
WBC Count	8.5 ± 4.9	8.3 ± 4.2	0.791

N (%)	Use of CCB		P for Difference
	YES(n = 162)	NO(n = 1110)	
HCT	0.36 ± 0.05	0.36 ± 0.05	0.966
Hypertension	162(100.0)	140(12.6)	< 0.001
Use of Beta Blockers	7(4.3)	35(3.2)	0.437
Use of ACEIARB	10(6.2)	74(6.7)	0.813
Use of Diuretics	2(1.2)	4(0.4)	0.171
Operation manner			
Two-incision	95(58.6)	684(61.6)	0.467
Three-incision	67(41.4)	426(38.4)	
Postoperative Chemotherapy	42(25.9)	342(30.8)	0.206
Postoperative Radiotherapy	26(16.0)	184(16.6)	0.866

Propensity-score matching analysis successfully created 155 pairs of patients. The baseline characteristics of these patients are shown in Table 2. Apart from a history of hypertension, all other baseline characteristics were balanced between the two groups, and all of the standardized differences were < 25%.

Table 2
Characteristics of CCB users and Non CCB users With Esophageal Cancer in the propensity matched cohort

N (%)	Use of CCB		P for Difference	Standardized Difference (%)
	YES(n = 155)	NO(n = 155)		
Age at diagnosis	63.5 ± 8.3	62.3 ± 9.2	0.240	13.7
Sex				
Male	123(79.4)	122(78.7)	0.889	1.4
Current Or Recent Cigarette Smoker	97(62.6)	95(61.3)	0.815	2.2
Current Or Recent Alcohol intake	50(32.3)	58(37.4)	0.340	-8.8
BMI (kg/m2)	22.0 ± 3.2	22.1 ± 2.9	0.771	-3.3
Clinical stage at diagnosis				
I	23(14.8)	25(18.1)	0.135	-8.9
II	53(34.2)	68(43.9)		-19.9
III	79(51.0)	62(40.0)		22.2
Primary cancer site				
upper segment	11(7.1)	5(3.2)	0.601	17.7
middle segment	96(61.9)	103(66.5)		-9.6
inferior segment	48(31.0)	47(30.3)		1.5
Histological type				
squamous carcinoma	147(94.8)	146(94.2)	0.803	2.2
Tumor Differentiation				
Poorly differentiated	62(40.0)	69(44.5)	0.499	-9.1
moderately differentiated	74(47.7)	68(43.9)		7.6
high differentiated	19(12.3)	18(11.6)		2.2
Diabetes	16(10.3)	15(9.7)	0.850	1.6

The propensity score was calculated with consideration for all baseline variables except for history of hypertension

N (%)	Use of CCB		P for Difference	Standardized Difference (%)
	YES(n = 155)	NO(n = 155)		
Chronic Lung Dis	21(13.5)	16(10.3)	0.381	7.9
Cerebrovascular Dis	5(3.2)	3(1.9)	0.720	6.5
CHD	1(0.6)	4(2.6)	0.371	-14.7
WBC Count	8.4 ± 4.6	7.9 ± 3.4	0.374	12.4
HCT	0.36 ± 0.05	0.36 ± 0.05	0.769	0.0
Hypertension	155(100.0)	25(16.1)	< 0.001	
Use of Beta Blockers	6(3.9)	7(4.5)	0.777	-2.5
Use of ACEIARB	9(5.8)	12(7.7)	0.498	-6.3
Use of Diuretics	1(0.6)	1(0.6)	1.000	0.0
Operation manner				
Two-incision	89(57.4)	102(65.8)	0.129	-14.1
Three-incision	66(42.6)	53(34.2)		
Chemotherapy	40(25.8)	39(25.2)	0.896	1.1
Radiotherapy	24(15.5)	16(10.3)	0.175	12.4
The propensity score was calculated with consideration for all baseline variables except for history of hypertension				

Postoperative Outcomes:

Overall, 42.9% of all 1272 patients who underwent esophagectomy experienced at least one postoperative complication, including thoracotomy, anastomotic leakage, anastomotic stenosis, postoperative pneumonia, and cardiac complications. The incidence of postoperative complications in patients who received preoperative CCBs was 45.7% compared with 42.5% in patients who did not receive CCBs (P=0.449). In the entire cohort, the unadjusted univariate analysis showed that there was no significant difference in any postoperative complications or other outcomes (Table 3) between the 2 groups. Table 3 (the right 3 columns) also presents the results of the multivariate analysis that assessed independent risk factors for postoperative complications in the propensity-matched cohort. Even after adjusting for propensity scores and covariates, preoperative CCBs use did not have a significant effect on

postoperative complications or other outcomes. The independent risk factors for postoperative outcomes are shown in fig 3A.

Overall survival:

The overall mortality rate before (38.3% vs 39.5%, P=0.756) or after matching (38.1% vs 31.6%, P=0.233) was not significantly different between the two groups. The Kaplan-Meier survival estimates of overall survival for the CCB and non-CCB groups are shown in Fig. 2Aand 2B. There were no significant differences between the CCB and non-CCB groups in overall survival (P = 0.160, log-rank test) (Fig. 2A), with an unadjusted estimated HR of 1.208 (95% CI: 0.925–1.578) in the entire cohort. After propensity matching, the use of preoperative CCBs was associated with reduced overall survival (P = 0.030, log-rank test) (Fig. 2B), with an estimated HR of 1.517 (95% CI, 1.036–2.220).

The results of the univariable and multivariable Cox regression analyses of overall survival after esophagectomy in the propensity-matched cohort are shown in Fig. 3B. Significant variables with p <0.1 in the univariable analysis were used in the multivariable analysis. In the multivariable Cox regression analysis, the effect of using preoperative CCBs on overall survival was still significant (HR 1.659, 95% CI: 1.123-2.450, P = 0.011). In addition, a history of smoking cigarettes (HR 1.605, 95% CI: 1.056-2.411, P = 0.027), clinical stage III at diagnosis (HR 1.975, 95% CI: 1.127-3.461, P = 0.017), preoperative use of diuretics (HR 5.278, 95% CI: 1.246-22.351, P=0.024), operation manner (HR 0.662, 95% CI: 0.442-0.992, P = 0.046) and chemotherapy (HR 0.431, 95% CI: 0.266-0.732, P = 0.002) were found to affect the overall survival of patients after esophagectomy.

Recurrence-Free Survival:

The recurrence rate of the CCB group was higher than that of the non-CCB group (43.8% vs 35.3%, P=0.035) before matching. However, the difference in recurrence rate between the two groups was not statistically significant after matching (43.2% vs 32.9%, P = 0.061). There was a significant difference between the CCB and non-CCB groups in recurrence-free survival (P =0.025, log-rank test) (Fig. 2C), with an unadjusted estimated HR of 1.330 (95% CI, 1.032–1.713) in the entire cohort. After propensity matching, the use of preoperative CCBs was not associated with a significant difference in recurrence-free survival (P = 0.054, log-rank test) (Fig. 2D), with an estimated HR of 1.425 (95% CI, 0.989–2.053).

The results of the univariable and multivariable Cox regression analyses of recurrence-free survival after esophagectomy in the propensity-matched cohort are shown in Fig. 3C. Significant variables with p <0.1 in the univariable analysis were used in the multivariable analysis. In the multivariable Cox regression analysis, the effect of using preoperative CCBs on recurrence-free survival was not significant (HR 0.618, 95% CI: 0.271-1.411, P = 0.253). However, a history of chronic lung disease (HR 1.679, 95% CI: 1.034-2.727, P =0.036), hypertension (HR 1.597, 95% CI: 1.087-2.345, P=0.017), and the use of preoperative

beta-blockers (HR 0.301, 95% CI: 0.094-0.962, P =0.043) were found to affect recurrence-free survival in patients after esophagectomy.

Discussion

Overall survival

From this observational study of 2415 patients with esophageal cancer, we found that the preoperative use of CCBs was significantly associated with a poor outcome in overall survival. Compared with the non-CCB group, the relative risk for overall mortality was 1.659 (95% CI: 1.123–2.450) in the CCB group. Our results are consistent with those of previous clinical studies (18, 19, 22). A population-based observational study from Sweden in 2002 indicated hypertensive patients who used CCBs had a higher mortality risk (HR:1.84,95% CI:1.25–2.72) and a higher cardiovascular morbidity risk (HR:2.37,95% CI:1.27–4.44) than those who did not use CCBs (18); Holmes et al. found that breast cancer patients treated with CCBs had an increased incidence of death compared to those who were not treated with CCBs (HR: 1.22, 95% CI: 1.02–1.47) (22). Moreover, a large Chinese population cohort study in 2015 that included 217,910 patients showed a significant association between CCBs and cancer mortality, and patients prescribed CCBs were more likely to die from cancer than those prescribed beta-blockers (adjusted HR: 1.406, 95% CI: 1.334–1.482, P < 0.001) (19).

In the past decade, CCBs have been suggested to affect the survival outcomes in cancer patients by interfering with biological processes such as apoptosis or cell differentiation(15). These results have been supported by several pieces of experimental evidence. For example, nifedipine was found to promote the proliferation and migration of breast cancer cells (17). However, the results of clinical studies investigating the association between CCBs and cancer are controversial. Rotshild V et al. suggested that exposure to CCBs is associated with an elevated risk of lung cancer (23). A large observational study published in 2013 also suggested that the use of CCBs for 10 years was related to a risk of breast cancer (3). However, some studies showed that CCB use was not associated with an elevated risk of breast cancer (24, 25). Sun et al. found that no association existed between CCBs and survival in cancer patients (26). The different results in these studies may be explained by different tumor types, population subgroups, or sample sizes. However, data on specific tumor types, such as esophageal cancer, have never been considered.

A history of smoking cigarettes and a highly advanced tumor stage are the other two risk factors that affect overall survival in this study and are well known for a poor prognosis (27). In addition, in our study, the type of operation to dissect three lymph nodes and postoperative chemotherapy could improve overall survival in patients who underwent esophagectomy, which is consistent with the meta-analysis conducted by Pasquali et al. (28).

Recurrence-free Survival

Although no association between the use of CCBs and recurrence-free survival of patients who underwent esophagectomy was observed in our study, surprisingly, beta-blockers played a role in prolonging the recurrence-free survival of esophageal cancer patients. A cohort study conducted in Norway with 3561 prostate cancer patients with high-risk or metastatic disease showed that beta-blocker use was associated with reduced prostate cancer mortality and reduced prostate cancer-specific mortality (29). Another large population-based cohort study of patients with colorectal cancer in Germany indicated that beta-blocker use was associated with prolonged overall survival and colorectal cancer-specific survival in stage IV patients (10). Overall, these findings are in accordance with ours (7, 10, 29). Our study showed that a history of chronic lung disease was associated with poor recurrence-free survival, which could be because patients with a history of chronic lung disease were more likely to be complicated with other diseases and poor physical conditions (30).

In this study, hypertension did not affect the overall survival of patients with esophageal cancer but was an independent risk factor for recurrence-free survival when propensity-score matching was applied. Several studies have reported that regardless of the use of antihypertensive drugs, hypertension was associated with a modestly increased risk of cancer and mortality from cancer (31, 32). Dyer et al. suggested that the potential of hypertension was a risk for cancer in patients with a blood pressure increase (i.e., relative risk of 2.2 with blood pressure > 148 mmHg and 3.05 with blood pressure > 160 mmHg) (33). However, the reports on the association between hypertension and cancer had inconsistencies. A cohort study found no association between blood pressure and subsequent cancer incidence or mortality (34). The organs most frequently cited regarding the association between hypertension and cancer incidence or mortality were the kidney (34), colon (33), breast (35) and endometrium (36), but the esophagus was seldomly mentioned in previous studies.

Postoperative Outcomes

Esophagectomy has historically been the primary curative treatment for esophageal cancer (37). The incidence of postoperative complications varies from 28–36% among different health centers (38). In this study, no significant association was found between CCBs usage and postoperative outcomes. However, as other studies that clinical stage III at diagnosis and operation type were found to be related to poor overall postoperative complications (39, 40).

Limitation

This study also has some limitations. First, this study was constrained by being retrospective in nature. Second, as a single-center observational study, avoiding selection bias is difficult. However, applying propensity-score matching was the best solution in this study and could balance covariates between the two groups to make the analyses comparable to a quasi-randomized experiment. Third, since the majority of the CCBs users were on nifedipine, the results should be generalized to other CCBs with caution.

Conclusion

In conclusion, after performing propensity-score matching analyses, this study suggests that patients with esophageal cancer who received CCBs preoperatively have shortened overall survival after esophagectomy compared to those who did not receive CCBs. However, there is no association between CCBs usage and recurrence-free survival or the incidence of postoperative complications for patients undergoing esophagectomy.

Abbreviations

CCBs= calcium channel blockers; IRB= institutional review board; CI= 95% confidence interval; OR= odds ratio; HD= hazards ratios;

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Sun Yat-Sen University Cancer Center review board. The study protocol was granted exemption from written informed consent (not human subjects research) by the Sun Yat-Sen University Cancer Center review board.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the www.researchdata.org.cn

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions:

Qihua Lin: This author helped conduct the study, analyze the data, and write the manuscript.

Tianhua Zhang: This author helped conduct the study, analyze the data, and write the manuscript.

Zhijie Wu: This author helped conduct the study, analyze the data, and write the manuscript.

Huiting Li: This author helped collect the data.

Junjie Yu: This author helped collect the data and analyze the data.

Hongying Tan: This author helped conduct the study.

Wenqian Lin: This author helped conduct the study.

Longhui Cao: This author helped design the study, conduct the study, analyze the data, and write the manuscript

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Figures

Fig.1 Study overview

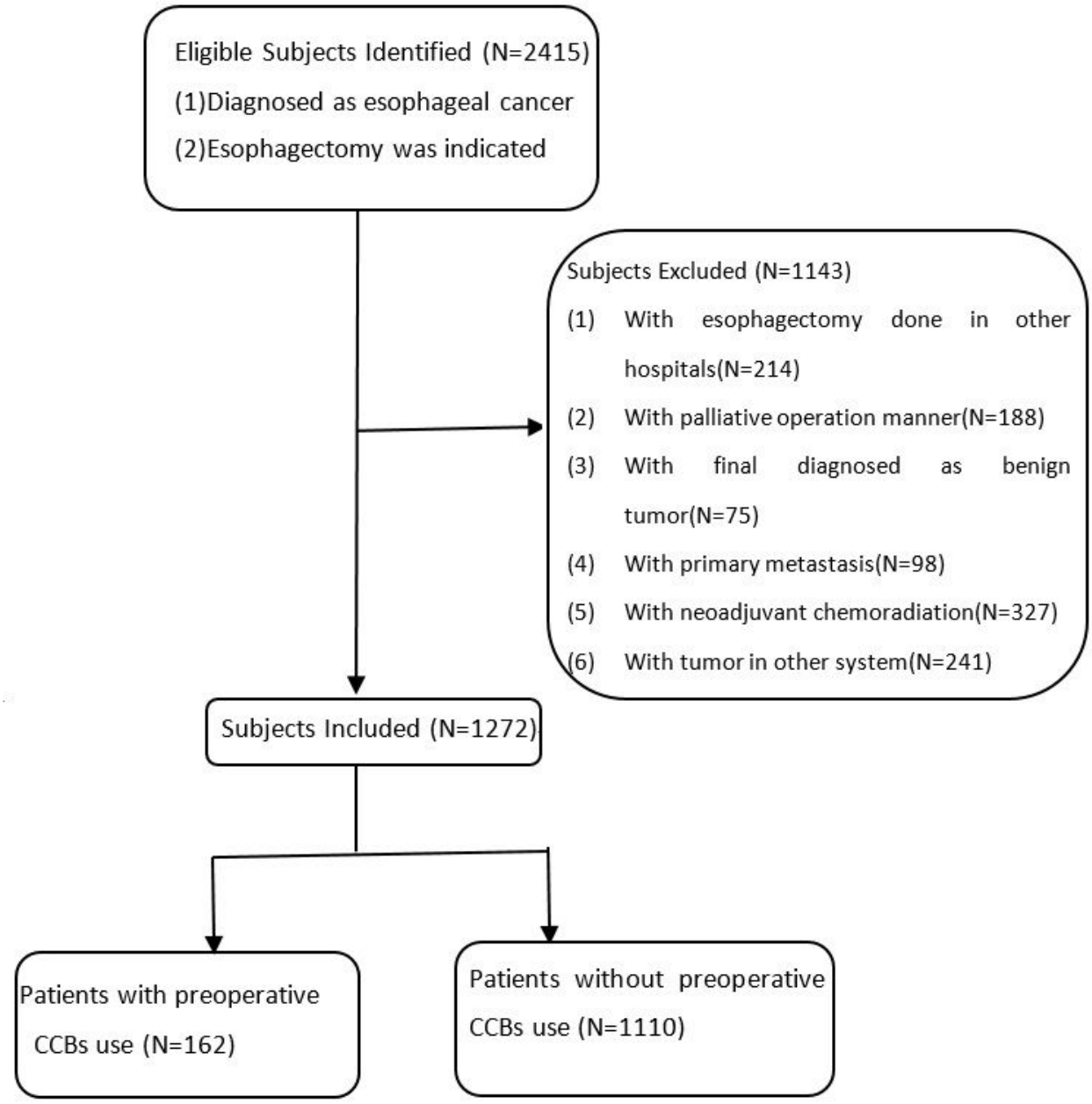

Figure 1

Study overview

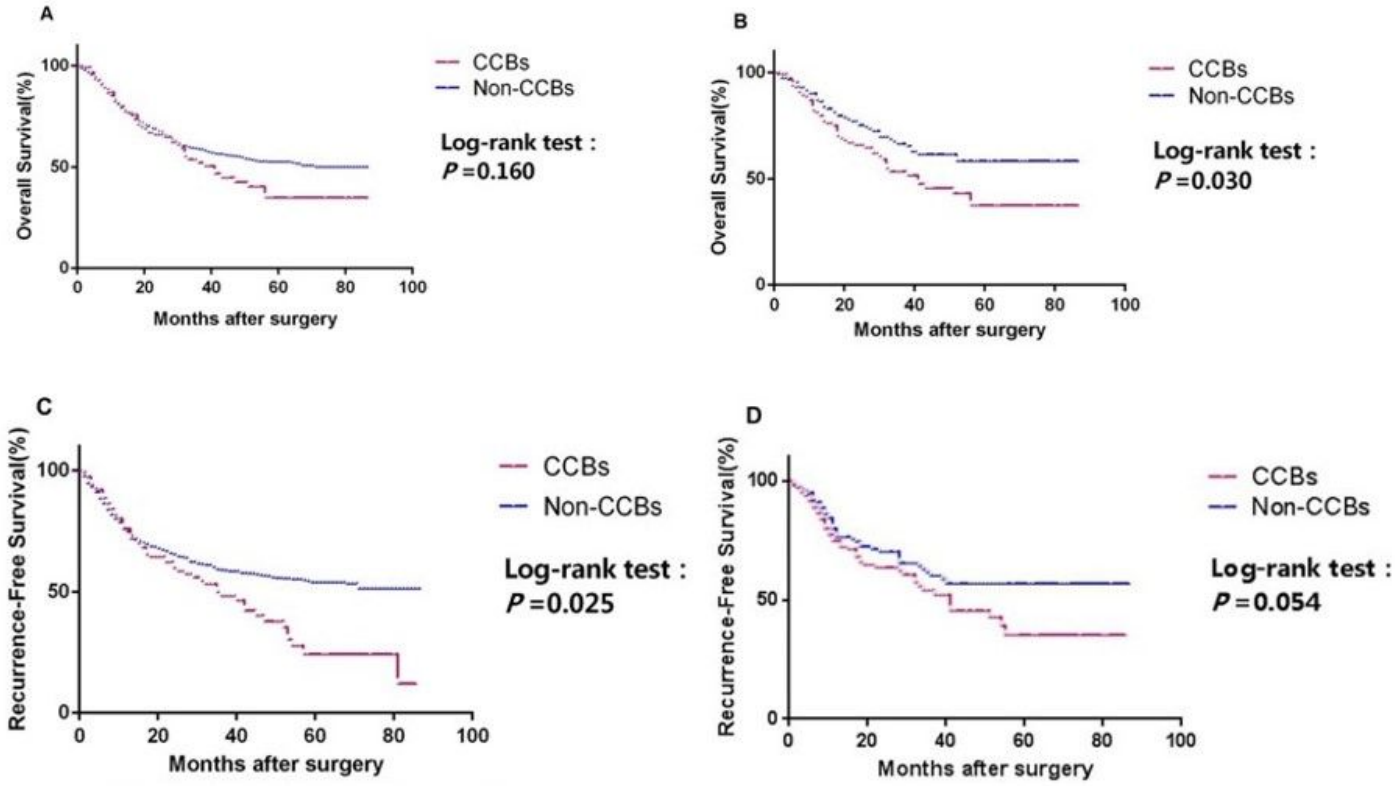

Figure 2. (A) Over-all Survival Curve of CCBs and Non-CCBs group in the entire cohort.(B) Over-all Survival Curve of CCBs and Non-CCBs group in the propensity matched cohort.(C) Recurrence-free Survival Curve of CCBs and Non-CCBs group in the entire cohort.(D) Recurrence-free Survival Curve of CCBs and Non-CCBs group in the propensity matched cohort.

Figure 2

2A Over-all Survival Curve of CCBs and Non-CCBs group in the entire cohort; 2B Over-all Survival Curve of CCBs and Non-CCBs group in the propensity matched cohort; 2C Recurrence-free Survival Curve of CCBs and Non-CCBs group in the entire cohort; 2D Recurrence-free Survival Curve of CCBs and Non-CCBs group in the propensity matched cohort

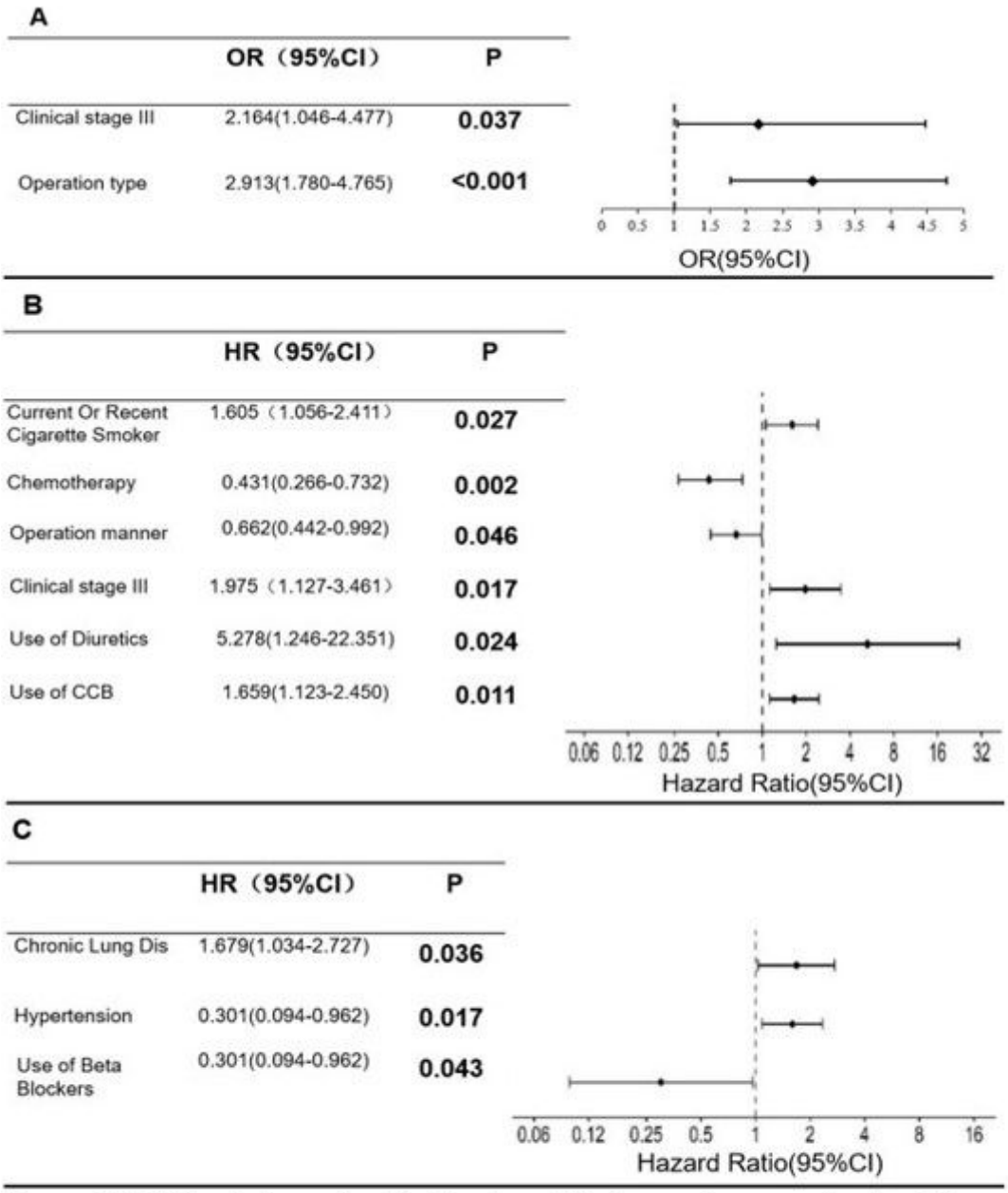

Figure 3.(A) The independent risk factors of Perioperative-complication.(B) Hazard Ratio of multivariable Cox regression analyses for Overall Survival in the propensity matched cohort.(C) Hazard Ratio of multivariable Cox regression analyses for Recurrence-Free Survival in the propensity matched cohort.
Significant variables with p <0.1 in the univariable analysis were used in the multivariable analysis.

Figure 3

3A The independent risk factors of Perioperative-complication; 3B Hazard Ratio of multivariable Cox regression analyses for Overall Survival in the propensity matched cohort; 3C Hazard Ratio of multivariable Cox regression analyses for Recurrence-Free Survival in the propensity matched cohort