Angiotensin II Receptor Blockers Improve Survival in Patients With Locally Advanced Oral Squamous Cell Carcinoma- A Propensity-Score-Matched Study

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Research Article

Keywords: angiotensin II receptor blockers, advanced oral squamous cell carcinoma, overall survival, disease-specific survival

Posted Date: January 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-136741/v1

Abstract

Objectives: Angiotensin II receptor blockers (ARBs) improve the survival rates of patients with various cancers. However, it remains unclear whether ARBs confer a survival benefit on patients with oral squamous cell carcinoma (OSCC). Here, we assessed the associations between ARB use and survival in patients with OSCC of different stages.

Materials and Methods: This was a 10-year retrospective cohort study of OSCC patients. We enrolled 7,763 patients diagnosed with oral cancer between January 2007 and December 2017 whose details had been entered into the Chang Gung Research Database. A total of 930 patients receiving surgery were recruited from the Chang Gung Research Database after performing 1:4 propensity score-matching between ARB users and non-users. Cox's regression models with adjusted covariates were employed to detect factors influencing the survival rates of patients with OSCC.

Results: Kaplan-Meier analysis revealed that the overall survival(OS) and disease-specific survival (DSS) rates of 180-day ARB users increased. Cox's regression models indicated that ARB use, early-stage OSCC, and only surgical intervention were independently prognostic of improved OS and DSS. An increased survival rate was also observed in 180-day ARB users in the stage III, Iva, and IVb categories.

Conclusions: ARB use for more than 180 days is associated with an increased survival rate and is a positive, independent prognostic factor in patients with OSCC. These findings highlight the clinical usefulness of ARBs in OSCC patients with advanced disease.

Introduction

Oral cancer is one of the most frequently occurring cancers worldwide. Oral squamous cell carcinoma (OSCC) represents the most common type of oral cancer, constituting approximately 90% of all oral cancers [1]. In 2018, more than 355,000 individuals were diagnosed with oral cancer worldwide, and approximately 177,000 oral cancer-related deaths were reported [2]. Despite advances in surgical techniques and chemoradiotherapy, the prognosis of patients with OSCC remains unsatisfactory, especially for those diagnosed with advanced disease. Therefore, the identification of novel therapeutic targets in OSCC is of high clinical importance.

The renin-angiotensin system (RAS) is involved in the regulation of blood pressure. Therefore, angiotensin I-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs) are among the most widely used anti-hypertensive drugs. A retrospective cohort study conducted by Lever and colleagues showed that the long-term ACEI use protected against cancer [3], suggesting that the local RAS played roles in tumor development and progression. Additionally, the RAS has been implicated in most human cancers; thus, the use of ACEIs/ARBs has been proposed as a promising anti-tumor strategy, which could potentially suppress tumor progression through inhibition of cancer cell proliferation and neovascularization [4]. Indeed, the combination of ACEIs/ARBs with conventional anti-cancer therapies has

been shown to improve clinical outcomes of patients with various types of cancer, including lung, urothelial, breast, and esophageal cancers [5–8].

However, the clinical usefulness of RAS inhibitors in patients with OSCC remains unclear. Also, most previous studies did not separately evaluate the anti-neoplastic effects of ACEIs and ARBs; the drug classes were combined when exploring the clinical outcomes of cancer patients. The effects of ARBs alone were inconsistent[9,10], suggesting that the ACEIs exerted all of the observed anti-neoplastic effects. Thus, we investigated the efficacy of ARBs in patients with OSCC receiving surgery. We used the Chang Gung Memorial Hospital database to perform a 10-year, retrospective cohort study. Furthermore, we explored the effects of ARBs on patients with advanced-stage OSCC.

Material And Methods

Study cohort

We enrolled 7,763 patients diagnosed with oral cancer between January 2007 and December 2017 whose details had been entered into the Chang Gung Research Database [11–13]. Figure 1 is a flow chart of the cohort study design for statistical analysis. Among the 7763 oral cancer patients, a total of 1560 patients were not recruited after applying the exclusion criteria. We performed propensity score-matching to balance covariates between ARB users and non-users. Hence, data from 930 patients were analyzed in our study, including 186 patients treated with ARBs and 744 matched patients who did not receive ARBs. This retrospective cohort study was approved by the Institutional Review Board (IRB) of Kaohsiung and Chiayi Chang Gung Memorial Hospital (approval nos. 202001463B0 and 201700253B0C602), and all experiments were performed in accordance with relevant guidelines and regulations. The Chang Gung Medical Foundation IRB (approval nos. 202001463B0) approves the waiver of the participants' consent.

Figure 1.

Statistical Analysis

Categorical data (e.g., sex, comorbidities, lifestyle risk factors, cancer sites, and AJCC stage) were analyzed using a two-sided Fisher's exact test or a two-sided Pearson's chi-squared test. Parametric and non-parametric continuous data were analyzed using Student's *t*-test and the Mann–Whitney *U* test, respectively. To minimize the confounding effects due to non-randomized allocation, data were analyzed from a 1:4 propensity score-matched cohort (ARBs vs. nil), which had been identified by the Greedy method with a 0.25 caliper width using NCSS software, version 10 (NCSS Statistical Software, Kaysville, UT, USA). Propensity scores were calculated using a logistic regression model with sex, age, pathological AJCC stage, and the diagnostic year of OSCC as covariates (Table S1). In ARB users, we calculated the survival time from the day of OSCC diagnosis if ABR was already used or from the day of starting ARB use if the patient had not used it after OSCC diagnosis. Because the diagnostic years were matched in both groups, the calculated survival time in non-users started from the same day as its match to make

the comparison between the two groups fair. After adjustment for these confounding factors, the Kaplan–Meier method and the log-rank test were used to evaluate the effects of ARBs on the primary outcome. The correlations with different comorbidities were evaluated by Pearson's correlation coefficient to prevent multicollinearity before building a regression model (Figure S1). A Cox proportional hazards model tested the dependence of primary factors on other prognostic factors in multivariate survival modeling. A stratified analysis was performed and adjusted to analyze the efficacy of ARBs in patients at different pathological stages. All statistical analyses were performed using SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). *P*-values < 0.05 were considered statistically significant.

Results

Baseline clinicopathological characteristics of the study cohort are summarized in Table 1. Of the 930 patients with OSCC, 92.7% (n = 862) were men and 7.3% (n = 68) were women. The median age at diagnosis was 58 years, and the mean follow-up time was 62.4 months. Tongue (34.8%) and buccal mucosa (34.7%) were the most common tumor sites. Five hundred and eighty-two patients (62.6%) had early-stage cancer (stage I or II), while the remaining 348 patients (37.4%) had advanced stage tumors (stage III, IVA, or IVB). Six hundred and eight patients (65.4%) underwent surgery alone, and 322 (34.6%) underwent surgery plus adjuvant radiotherapy or concurrent chemoradiotherapy. At the end of the study period, 256 (27.5%) patients had died; 133 of these (14.3%) had died of primary head and neck cancer.

Table 1
Demographic and clinical characteristics of the study cohort

Variables	Cohort n = 930	ARBs ≥ 180 days n = 186	Non-Users n = 744	*p* value
Median age at diagnosis, years (IQR)	58 (52–66)	58 (52–65)	58 (52–66)	0.793
Gender	68 (07.3%)	13 (07.0%)	55 (07.4%)	0.850
Female	862 (92.7%)	173 (93.0%)	689 (92.6%)	
Male				
Tumor sites	65 (07.0%)	12 (06.5%)	53 (07.1%)	0.309
Lip	324 (34.8%)	61 (32.8%)	263 (35.3%)	
Oral tongue	103 (11.1%)	16 (08.6%)	87 (11.7%)	
Upper/lower Gum	34 (03.7%)	7 (03.8%)	27 (03.6%)	
Floor of mouth	323 (34.7%)	77 (41.4%)	246 (33.1%)	
Buccal mucosa	15 (01.6%)	1 (00.5%)	14 (01.9%)	
Hard palate	46 (04.9%)	10 (05.4%)	36 (04.8%)	
Retromolar trigone	20 (02.2%)	2 (01.1%)	18 (02.4%)	
Unidentified				
Lifestyle Risk Factors (n = 921)				
Smoking	264 (28.7%)	58 (31.2%)	206 (28.0%)	0.395
No	657 (71.3%)	128 (68.8%)	529 (72.0%)	
Yes				
Betel nuts consumption	397 (43.1%)	82 (44.1%)	315 (42.9%)	0.762
No	524 (56.9%)	104 (55.9%)	420 (57.1%)	
Yes				
Alcoholic beverages	405 (44.0%)	78 (41.9%)	327 (44.5%)	0.531
No	516 (56.0%)	108 (58.1%)	408 (55.5%)	
Yes				
Comorbidities				

Variables	Cohort n = 930	ARBs ≥ 180 days n = 186	Non-Users n = 744	*p* value
Diabetes mellitus	706 (75.9%)	71 (38.2%)	635 (85.3%)	*<0.001
No	224 (24.1%)	115 (61.8%)	109 (14.7%)	
Yes				
Hypertension	633 (68.1%)	20 (10.8%)	613 (82.4%)	*<0.001
No	297 (31.9%)	166 (89.2%)	131 (17.6%)	
Yes				
Atrial fibrillation/flutter	908 (97.6%)	173(93.0%)	735(98.8%)	*<0.001
No	22 (02.4%)	13(07.0%)	9(01.2%)	
Yes				
Hyperlipidemia	739(79.5%)	67(36.0%)	672(90.3%)	*<0.001
No	191(20.5%)	119(64.0%)	72(09.7%)	
Yes				
Clinical AJCC 7th staging	242 (26.0%)	53 (28.5%)	189 (25.4%)	0.177
I	298 (32.0%)	68 (36.6%)	230 (30.9%)	
II	130 (14.0%)	20 (10.8%)	110 (14.8%)	
III	260 (28.0%)	45 (24.2%)	215 (28.9%)	
IVa & IVb				
Pathological AJCC 7th staging	313 (33.7%)	69 (37.1%)	244 (32.8%)	0.661
I	269 (28.9%)	53 (28.5%)	216 (29.0%)	
II	138 (14.8%)	27 (14.5%)	111 (14.9%)	
III	210 (22.6%)	37 (19.9%)	173 (23.3%)	
IVa & IVb				
Treatment	608 (65.4%)	125 (67.2%)	483 (64.9%)	0.558
Operation alone	322 (34.6%)	61 (32.8%)	261 (35.1%)	
Operation plus RT/CCRT				

Variables	Cohort n = 930	ARBs ≥ 180 days n = 186	Non-Users n = 744	*p* value
Recurrence	757 (81.4%)	157 (84.4%)	600 (80.6%)	0.238
No	173 (18.6%)	29 (15.6%)	144 (19.4%)	
Yes				
Survival	674 (72.5%)	151 (81.2%)	523 (70.3%)	*0.010
Alive	133 (14.3%)	16 (08.6%)	117 (15.7%)	
Primary OSCC related death	123 (13.2%)	19 (10.2%)	104 (14.0%)	
Die of other reasons				

Abbreviations: AJCC, American Joint Committee on Cancer; ARBs, angiotensin II receptor blockers; CCRT, concurrent chemoradiotherapy; IQR, interquartile range; OSCC, oral squamous cell carcinoma; RT, radiotherapy

ARB administration was significantly associated with underlying conditions, including diabetes mellitus, hypertension, atrial fibrillation/flutter, and hyperlipidemia. Otherwise, there were no statistically significant differences in clinical features between ABR-treated patients and those who did not receive ABRs (Table 1). A multivariate analysis revealed that advanced disease, and surgery plus adjuvant therapy were associated with reduced overall survival (OS) and disease-specific survival (DSS). Notably, 180-day ARB use was associated with improved overall survival (OS) ($HR_{ARB\ users\ vs.\ non-users}$ = 0.58, 95% CI = 0.38–0.90) and disease-specific survival (DSS) ($HR_{ARBs\ users\ vs.\ non-users}$ = 0.47, 95% CI = 0.25–0.87) in patients with resectable oral cancer (Table 2). In this 10-year cohort study, patients receiving ARBs for more than 180 days exhibited a significantly higher OS rate, compared to those who did not receive ARBs (Fig. 2). Similarly, the DSS rate was significantly higher in patients receiving ARBs than in those who did not receive ARBs (Fig. 3).

Table 2
Multivariate analysis of prognostic factors for OS and DSS in patients with oral cancer

Factor	OS		DSS	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age (year (IQR))	1.02 (1.00-1.03)	* 0.020	1.00 (0.99–1.02)	0.755
Gender	1	0.219	1	0.512
Female	0.76 (0.50–1.18)		0.81 (0.42–1.54)	
Male				
A*trial fibrillation*	1	0.397	1	0.240
No	1.34 (0.68–2.66)		0.31 (0.04–2.21)	
Yes				
Hypertension	1	0.392	1	0.840
No	0.87 (0.62–1.21)		1.05 (0.67–1.65)	
Yes				
Pathological AJCC 7th staging	1	*<0.001	1	*<0.001
I	1.01 (0.70–1.47)		1.17 (0.65–2.09)	
II	1.78 (1.19–2.67)		2.21 (1.20–4.06)	
III	2.55 (1.72–3.78)		3.31 (1.83–5.96)	
IVa & IVb				
Treatment	1	* 0.027	1	* 0.001
Operation alone	1.41 (1.04–1.91)		2.03 (1.31–3.13)	
Operation plus RT/CRT				
ARBs use	1	*0.014	1	* 0.016
No	0.58 (0.38–0.90)		0.47 (0.25–0.87)	
≥ 180 days				

Abbreviations: AJCC, American Joint Committee on Cancer; ARBs, angiotensin II receptor blockers; CRT, chemoradiotherapy; DSS, disease specific survival; OS, overall survival; RT, radiotherapy;

* $p \leq 0.05$

A survival benefit with at least 180 days of ARB use was observed in patients with stages III and IV OSCC, but no statistical significance was observed in patients with stages I and II OSCC in a stratified analysis (Tables 3 and 4). We also evaluated the effect of ARBs on the survival rates of advanced OSCC patients

in the T and N categories. The ARB treatment outcomes for OSCC patients in advanced T (T3 and 4) or either N category in terms of OS rate were significantly improved (Table S2). Overall, these stratified analyses suggested that patients with late-stage OSCC were the most likely to benefit from ARB use for more than 180 days after OSCC diagnosis.

Table 3
Effects of ARBs on disease specific survival in patients with early and advanced OSCC

Pathological AJCC staging	Variables	Primary OSCC related death	Alive or die of other reasons	Crude HR (95% CI)	*p*-value	**Adjusted HR (95% CI)	*p*-value
Stage I & II	**None**	40(08.7%)	420(91.3%)	1	0.192	1	0.429
	ARBs	7(05.7%)	115(94.3%)	0.59 (0.26–1.31)		0.68 (0.26–1.78)	
Stage III & IV	**None**	77(27.1%)	207(72.9%)	1	*0.012	1	*0.019
	ARBs	9(14.1%)	55(85.9%)	0.41 (0.21–0.82)		0.38 (0.17–0.85)	

Abbreviations: AJCC, American Joint Committee on Cancer; ARBs, angiotensin II receptor blockers; HR, Hazard Ratio; OSCC, oral squamous cell carcinoma;

* $p \leq 0.05$

** Model was adjusted for age, gender, treatment and comorbidities (atrial fibrillation and hypertension).

Table 4
Effects of ARBs on overall survival in patients with early and advanced OSCC

Pathological AJCC staging	Variables	Death	Alive	Crude HR (95% CI)	*p*-value	**Adjusted HR (95% CI)	*p*-value
Stage I & II	**None**	93(80.9%)	367(78.6%)	1	0.288	1	0.676
	ARBs	22(19.1%)	100(21.4%)	0.78 (0.49–1.24)		0.88(0.48–1.61)	
Stage III & IV	**None**	128(90.8%)	156(75.4%)	1	* <0.001	1	*0.003
	ARBs	13(9.2%)	51(24.6%)	0.35 (0.20–0.62)		0.37(0.19–0.71)	

Abbreviations: AJCC, American Joint Committee on Cancer; ARBs, angiotensin II receptor blockers; HR, Hazard Ratio; OSCC, oral squamous cell carcinoma;

* $p \leq 0.05$

** Model was adjusted for age, gender, treatment and comorbidities (atrial fibrillation and hypertension).

Discussion

To the best of our knowledge, this was the first study to investigate the potential clinical benefit of ARBs in patients with OSCC receiving surgery. In this 10-year retrospective cohort study, patients who received ARBs for at least 180 days had improved OS and DSS, compared to patients who did not receive ARBs. In addition, patients with locally advanced OSCC experienced the greatest benefit from ARBs.

The RAS consists of several enzymatic and non-enzymatic protein components and is essential for maintenance of vascular homeostasis. Angiotensinogen is produced in the liver and cleaved by the aspartyl protease renin to angiotensin I. Angiotensin I is subsequently cleaved by the angiotensin I-converting enzyme to produce angiotensin II (Ang II). Ang II is a key component of the RAS, which exerts its actions by binding to two G protein-coupled receptors: angiotensin receptor 1 (AT1R) and the lesser known angiotensin receptor 2 [14]. It is increasingly evident that, in addition to systemic effects on blood pressure and fluid homeostasis, AT1R and Ang II have important roles at the local tissue level. AT1R overexpression has been reported in numerous cancers, including ovarian, breast, and bladder cancer [15,16]. Consistent with these findings, ARBs and ACEIs have been reported to reduce tumor growth and vascularization in a wide range of cancers, suggesting a role for Ang II in cancer development and progression [4].

Several clinical studies have suggested a role for the RAS in terms of the effectiveness of anti-cancer therapies [17–19]; however, the clinical utilities of ARBs alone have not been reported. Although a nationwide population-based study showed that long-term ARB use was associated with a lower incidence of cancer [9], a meta-analysis of randomized controlled trials found that ARBs were associated with a modest increase in cancer risk [10]. The ARB Trialists Collaboration study and a recent meta-analysis concluded that ARB use had no effect on cancer incidence [20,21]. Briefly, the varying extent of concurrent ACEI use among the studies may explain the discrepancies. We evaluated patients who had received ARBs only (Table S3).

Head and neck cancer is the sixth most common cancer worldwide [22]. The critical role of RAS in head and neck cancer has been shown in various tissues, including the oral mucosa [23]. Additionally, the ACEI perindopril has been shown to reduce the growth of head and neck squamous cell carcinoma (HNSCC) *in vivo* [24], suggesting a role for Ang II in HNSCC. Ang II also has been found to promote HNSCC cell migration and invasion [25]. The effects of Ang II on autocrine and paracrine signaling pathways are mediated by AT1R, suggesting that ARBs might provide a clinical benefit in patients with HNSCC.

However, no large study has yet shown that ARBs improve the clinical outcomes of patients with head-and-neck cancer.

We found that ARB use for at least 180 days improved the 10-year OS and DSS rates of patients with OSCC (Figs. 2 and 3); the effects were most pronounced for patients with late-stage resectable OSCC (Tables 3 and 4). This was also true of subgroups of patients defined via TN staging; ARB use was associated with increased survival of patients with advanced T (T3 and 4) category (Table S2). As T refers to local tumor containment, the data suggest that ARBs are beneficial for patients with locally advanced OSCC. It remains unclear how ARBs affect OSCC progression and improve survival rates. An prior in vitro study might explain this effect: co-injection of cancer cells with stromal cells increased tumor size and fibrosis; ARB treatment attenuated these effects [26].

Our study had a few limitations. First, medical records were incomplete for some patients. Therefore, some critical clinicopathological characteristics (e.g., surgical margin, extranodal extension, and depth of tumor invasion) could not be analyzed in our study. However, the large cohort size supported the validity of conclusions drawn for the assessed clinicopathological characteristics. Second, although our study included only data from patients treated with ARBs, a considerable proportion of the patients were receiving concurrent treatment with other agents to control hypertension, which might have influenced our findings. Several patients received amlodipine and hydrochlorothiazide (Table S3); however, there is no evidence that these agents suppress cancer development or progression [27 28]. Therefore, we presume that treatment with these agents had a minimal influence on our findings. Third, various ARBs were included; therefore, the standardized effective dosage was difficult to calculate and the dose effect could not be measured. On the other hand, the use of propensity score matching (PSM) and the large database were highlights of our study. PSM attempts to reduce the bias due to confounding variables that can arise if the effects of treatment are assessed simply by comparing outcomes between patients that received the treatment versus those that did not. We created a 1:4 propensity-score-matched study group to minimize any confounding effect of non-randomized allocation when comparing the groups.

Conclusion

This was the first study to investigate the clinical usefulness of ARBs in patients with OSCC receiving surgery. Patients who received ARBs for at least 180 days exhibited improved OS and DSS. Additionally, ARBs provided a greater survival benefit in patients with operable stage III, IVa, and IVb OSCC, which highlights the clinical usefulness of ARBs in patients with OSCC, who are diagnosed with advanced disease.

Declarations

Author Contributions

Conceptualization, Methodology, Writing - Original Draft: C,-N,W; Software, Validation, Formal analysis: S,-C,W; Investigation, Resources: W,-C,C; Formal analysis, Data Curation: Y,-H,Y; Visualization: C,-Y,C; Data Curation: F,-M,F; Resources: S,-H,L; Writing - Review & Editing, Supervision, Visualization: S,-D,L; Project administration, Funding acquisition, Conceptualization: T,-J,C

Role of the Funding Source

This research was funded by Kaohsiung Chang Gung Memorial Hospital, Taiwan, CFRPG8H0401 and CORPG8J0091

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgement

We thank Jo-Chi Chin, Huei-Yi Kuo, the Health Information and Epidemiology Laboratory at the Chiayi Chang Gung Memorial Hospital and the Biostatistics Center at Kaohsiung Chang Gung Memorial Hospital for statistics work.

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/sDvE3w

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Figures

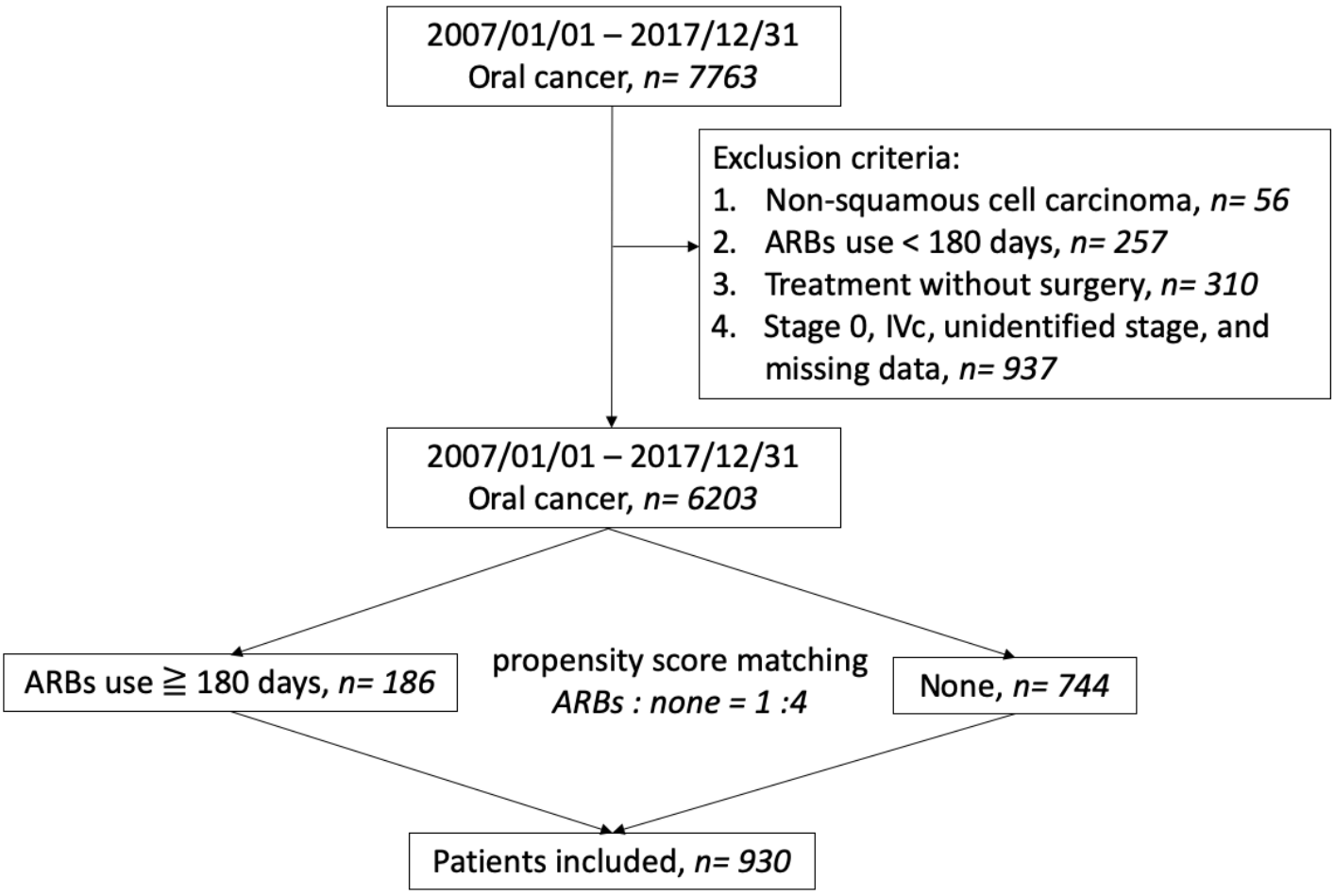
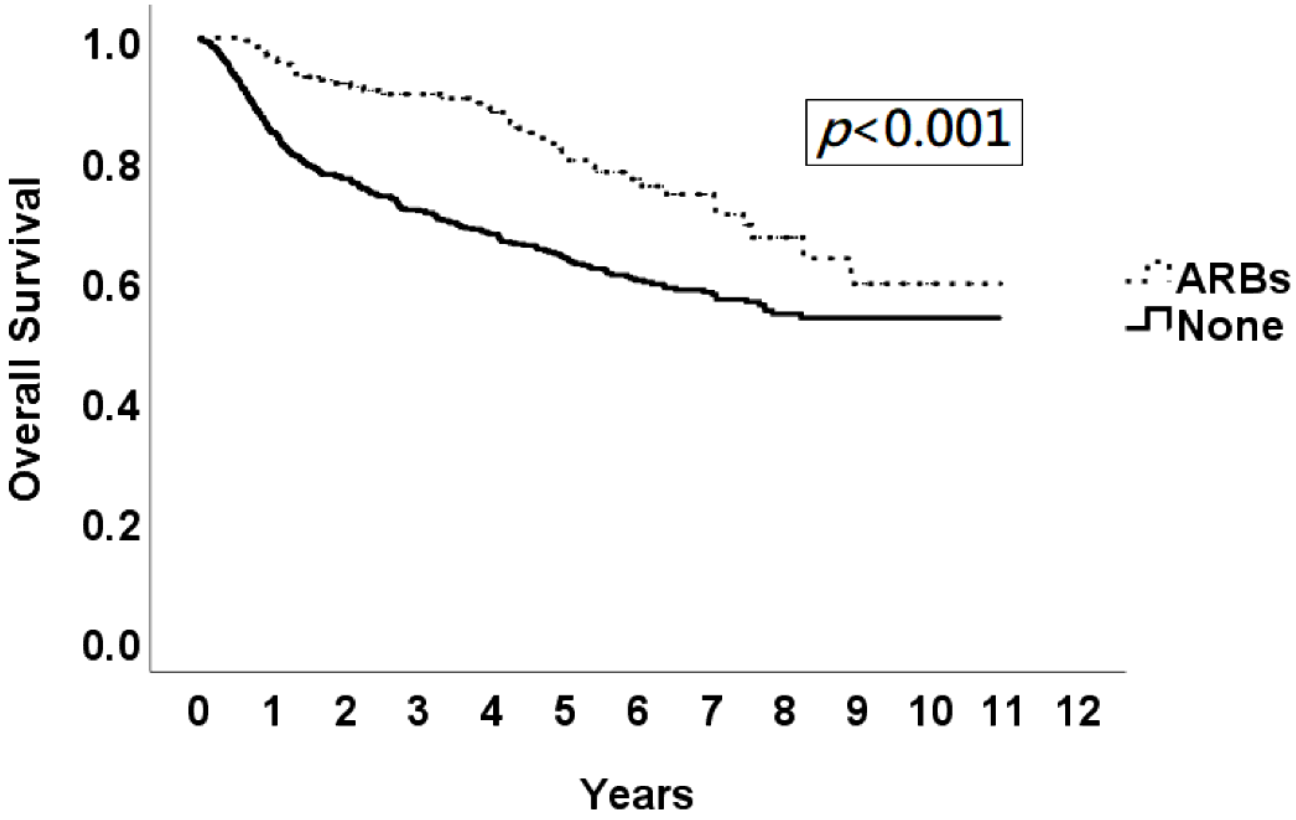


Figure 1

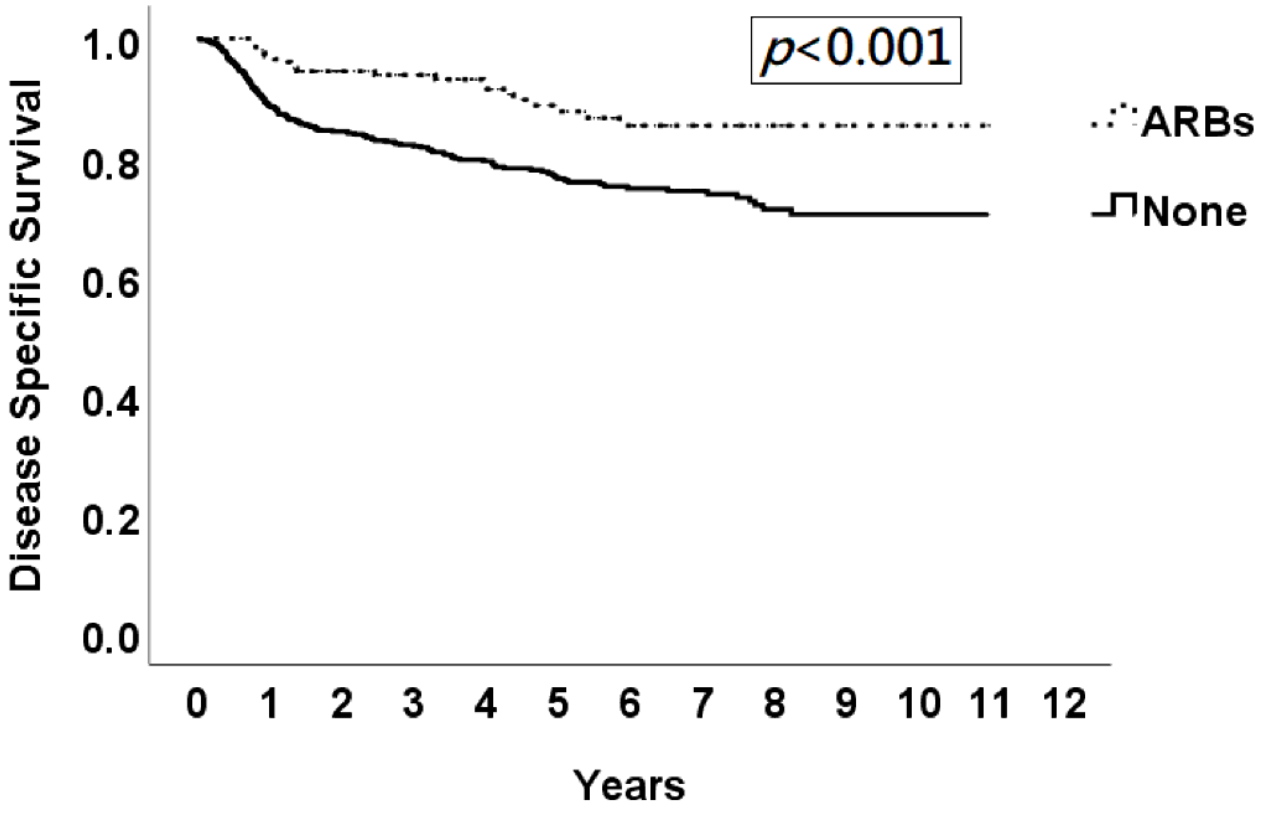
Flow diagram illustrating propensity score matching in patients with oral cancer. ARBs, angiotensin II receptor blockers



Variables	Cohort n=1015	Survival Rates (%) Years										*p* value
		1	2	3	4	5	6	7	8	9	10	
ARBs use												<0.001***
≧ 180 days	203 (20.0%)	94.0 186	92.1 178	89.9 147	82.8 128	79.5 100	76.7 74	68.2 54	61.0 35	61.0 16	61.0 7	
None	812 (80.0%)	79.5 744	74.6 650	70.3 501	66.3 400	62.7 302	60.6 215	56.7 153	55.9 94	55.9 54	55.9 23	

Figure 2

Kaplan–Meier survival curve of OS rates between angiotensin II receptor blockers users (≥ 180 days) and non-users. The estimated 5- and 10-year OS rates of ARB non-users (None) were 62.7% and 55.9%, respectively. The estimated 5- and 10-year OS rates of ARB users (≥180 days) were 79.5% and 61.0%, respectively. ARBs, angiotensin II receptor blocker; OS, overall survival



Variables	Cohort n=1015	Survival Rates (%) Years										*p* value
		1	2	3	4	5	6	7	8	9	10	
ARBs use												<0.001***
≧ 180 days	203 (20.0%)	94.3 186	93.6 178	91.4 147	87.7 128	85.4 100	85.4 74	85.4 54	85.4 35	85.4 16	85.4 7	
None	812 (80.0%)	84.2 744	81.9 650	79.1 501	76.2 400	74.6 302	74.2 215	71.2 153	70.2 94	70.2 54	70.2 23	

Figure 3

Kaplan–Meier survival curve of DSS rates between angiotensin II receptor blockers users (≧ 180 days) and non-users. The estimated 5- and 10-year DSS rates of ARB non-users (None) were 74.6% and 70.2%, respectively. The estimated 5- and 10-year DSS rates of ARB users (≧180 days) were 85.4% and 85.4%, respectively. ARBs, angiotensin II receptor blockers; DSS, disease-specific survival

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplement20201229.pdf