Heliyon 10 (2024) e34168

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Combined radiation and chemotherapy versus monotherapy for anaplastic thyroid cancer: A SEER retrospective analysis

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ARTICLE INFO

Keywords:
Anaplastic thyroid cancer
Chemotherapy
SEER
Radiotherapy
Survival

ABSTRACT

Background: The effect of combined radiation and chemotherapy (combination therapy) versus monotherapy on anaplastic thyroid carcinoma (ATC) has not yet been clear.
Methods: We identified 516 ATC patients during 2010–2015 from the Surveillance, Epidemiology and End Results (SEER) database and evaluated their survival outcome using the Kaplan-Meier method, Cox regression analysis and propensity score matching (PSM) technique.
Results: The median overall survival (OS) among the entire cohort was 3 months (95 % confidence interval [CI], 2.58–3.42 months), and the 6- and 12-month OS rates were 29 % (95 % CI, 25.01%–32.88 %) and 13 % (95 % CI, 10.60%–16.58 %), respectively. Multivariable analysis demonstrated that ATC patients not receiving radiotherapy or chemotherapy were unquestionably associated with worse OS (hazard ratio [HR] 3.000, 95 % CI, 2.390–3.764) and cancer-specific survival (CSS) (HR = 3.107, 95 % CI, 2.388–4.043), compared with those receiving combination therapy. However, combination therapy did not predict better prognosis compared with monotherapy (all $P > 0.05$). After PSM, the median OS and CSS were also not significantly improved in patients undergoing chemoradiotherapy versus chemotherapy alone (OS, $P = 0.382$; CSS, $P = 0.420$) or radiotherapy alone (OS, $P = 0.065$; CSS, $P = 0.251$).
Conclusion: Combination therapy, compared to monotherapy, does not have the expected improvement in survival beyond the benefits achievable with each single-modality treatment, necessitating further prospective research to tailor its treatment management.

1. Introduction

Anaplastic thyroid carcinoma (ATC) originates from the follicular cells of the thyroid gland, and accounts for only about 1–2% of thyroid cancers, yet it is the most lethal variety among them [1,2]. It is critical to identify prognostic factors for ATC to risk-stratify patients and guide therapeutic and diagnostic decisions. Previous studies have reported the risk factors on survival in ATC such as older age, greater tumor size, and distant metastasis [3–7], however, many of them are inconsistent and hampered by selection bias and other study design constraints.

Due to the highly aggressive nature of ATC, single-modality treatment often yield limited effect on patient survival [8]. Previous

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https://doi.org/10.1016/j.heliyon.2024.e34168
Received 16 April 2024; Received in revised form 4 July 2024; Accepted 4 July 2024
Available online 5 July 2024

studies found that surgical resection followed by radiotherapy, sometimes in combination with chemotherapy, results in improved survival [9–12]. However, the impact of radiation and/or chemotherapy on the survival of ATC patients, despite their importance in multimodal therapy, remains a subject of debate and uncertainty [12–15]. A smaller population-based study conducted by the Mayo Clinic in 2017 on 48 ATC patients revealed that survival was improved in individuals who underwent surgery along with chemo-radiotherapy in patients with stage IVA/B, emphasizing the necessity of concurrent chemoradiation therapy [16]. Contrarily, Yau et al. reported that only the combination of surgical resection plus radiotherapy was an independent predictor of survival, but chemotherapy was not associated with increased survival using multivariate analysis [10]. Currently, the treatment guidelines and strategies are primarily based on the published data, which are either limited to older, single-institution studies with small cohorts, or there are always heterogeneity biases due to differences in patient characteristics from regions. Hence, a large population-based study that is generalizable to the population is required.

The surveillance, Epidemiology, and End Results (SEER) Program is a premier source for cancer statistics in the United States, providing information on the incidence, prevalence, and survival from specific geographic areas as well as aggregated reports on all this cancer mortality for the US. The purpose of this study is to identify the prognostic factors potentially affecting survival in ATC patients and further investigate the effect of combined chemoradiotherapy versus radiotherapy or chemotherapy alone on the survival outcome of ATC patients. Based on the SEER database data, we perform this study using multivariate Cox regression analysis and propensity score matching technique which has been proven to reduce or minimize the confounding that occurs frequently in observational studies of the effect of treatment on outcomes and has the best performance for estimating absolute effects of treatment on survival outcomes [17,18].

2. Methods

2.1. Patient collection

We retrieved data from the SEER Research Plus Data of the National Cancer Institute (http://seer.cancer.gov/) based on the November 2021 submission, which represented approximately 27.8 % of the US population. We identified ATC patients diagnosed between January 2010 and December 2015 using SEER*Stat software (version 8.4.1), which were retrieved according to the International Classification of Diseases for Oncology, third edition (ICD-O-3) site record for thyroid gland (C73.9). The ICD-O-3 codes for histologic type were 8020, 8021, 8030, 8031, 8032 and 8035. In this study, the tumor grading and staging of all ATC patients were classified according to the American Joint Committee on Cancer (AJCC) 6th edition guidelines.

We enrolled 551 patients with ATC diagnosed between 2010 and 2015. Patients who diagnosed with ATC by autopsy or death certificate were excluded, as were those with an unknown follow-up for survival analysis, or ambiguous “Caused of Death”. Consequently, a total of 538 patients diagnosed with ATC were preliminarily selected from the SEER database. In addition, 2 cases with missing data for “race” and 20 patients with "NOS (Not Otherwise Specified)" from the Derived AJCC Stage were eliminated. Eventually, the analytic cohort included 516 patients with ATC. The flow chart of the patient selection procedure in this study is shown in Fig. 1.

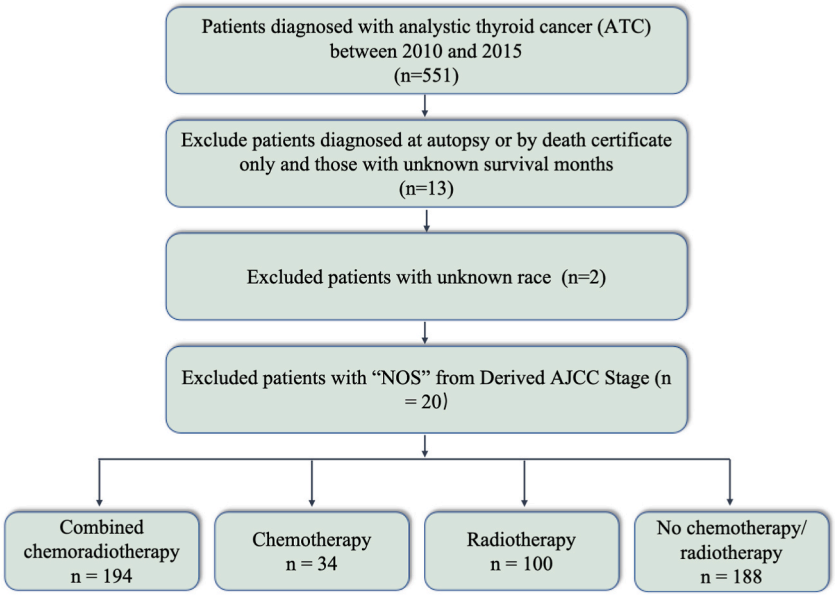

Fig. 1. Flow chart for patient selection procedure of the SEER data set.

Table 1
Univariate Cox analysis for Overall survival and Cancer-specific survival in patients with ATC.

Variables	Number (%) (=516)	Univariate analysis					
		Overall survival			Cancer-specific survival		
		Median OS(95%CI) (m)	HR(95%CI)	*P* Value	Median CSS(95%CI) (m)	HR(95%CI)	*P* Value
Age at diagnosis (years)							
<55	64 (12.4)	6.0 (3.466–8.534)	Reference		6.0 (3.183–8.817)	Reference	
≥55	452 (87.6)	3.0 (2.572–3.428)	1.443 (1.086–1.917)	0.011	4.0 (3.244–4.756)	1.107 (0.820–1.495)	0.507
Sex							
Female	307 (59.5)	3.0 (2.497–3.503)	Reference		4.0 (3.131–4.869)	Reference	
Male	209 (40.5)	3.0 (2.230–3.770)	0.909 (0.756–1.093)	0.311	5.0 (3.712–6.288)	0.931 (0.751–1.153)	0.510
Race							
White	409 (79.3)	3.0 (2.481–3.519)	Reference		5.0 (3.948–6.052)	Reference	
Black	43 (8.3)	2.0 (1.207–2.793)	1.466 (1.063–2.020)	0.020	3.0 (1.874–4.126)	1.689 (1.185–2.407)	0.004
Other	64 (12.4)	2.0 (0.918–3.082)	1.280 (0.971–1.687)	0.080	3.0 (1.752–4.284)	1.313 (0.953–1.809)	0.096
Tumor Size(cm)							
<6	210 (40.7)	5.0 (3.331–6.669)	Reference		7.0 (5.713–8.287)	Reference	
≥6	224 (43.4)	3.0 (2.476–3.524)	1.470 (1.203–1.797)	<0.001	3.0 (2.268–3.732)	1.861 (1.469–2.358)	<0.001
Unknown	82 (15.9)	1.0 (0.619–1.381)	2.094 (1.601–2.739)	<0.001	2.0 (0.941–3.059)	2.393 (1.739–3.294)	<0.001
AJCC Stage							
IVA	62 (12.0)	7.0 (5.338–8.662)	Reference		12.0 (5.333–18.667)	Reference	
IVB	202 (39.1)	4.0 (3.107–4.893)	1.299 (0.949–1.777)	0.102	7.000 (5.520–8.848)	1.598 (1.065–2.399)	0.024
IVC	252 (48.8)	2.0 (1.679–2.321)	2.293 (1.647–3.044)	<0.001	2.0 (1.394–2.606)	3.135 (2.110–4.658)	<0.001
N Stage							
N0	192 (37.2)	4.0 (3.604–5.396)	Reference		7.0 (5.311–8.689)	Reference	
N1	284 (55.0)	3.0 (2.497–3.503)	1.218 (1.003–1.480)	0.046	4.0 (3.412–4.588)	1.398 (1.110–1.760)	0.004
NX	40 (7.8)	1.0 (0.387–1.613)	1.912 (1.352–2.705)	<0.001	3.0 (1.977–4.023)	2.061 (1.367–3.105)	0.001
Distant metastasis							
No	250 (48.4)	5.0 (3.798–6.202)	Reference		8.0 (6.704–9.296)	Reference	
Distant mets without LN(s)	154 (29.8)	2.0 (1.455–2.545)	1.885 (1.523–2.333)	<0.001	3.0 (2.225–3.775)	2.205 (1.721–2.826)	<0.001
Distant mets with LN(s)	52 (10.1)	2.0 (1.319–2.681)	2.204 (1.608–3.020)	<0.001	2.0 (1.177–2.823)	2.896 (2.049–4.095)	<0.001
Other	60 (11.6)	1.0 (0.052–1.948)	1.839 (1.374–2.462)	<0.001	3.0 (1.823–4.177)	1.847 (1.295–2.635)	<0.001
Surgery							
No	249 (48.3)	2.0 (1.643–2.357)	Reference		3.0 (2.363–3.637)	Reference	
Lobectomy	93 (18.0)	3.0 (1.462–4.538)	0.590 (0.459–0.759)	<0.001	6.0 (4.249–7.751)	0.539 (0.400–0.726)	<0.001
Near/total thyroidectomy	167 (32.4)	6.0 (4.610–7.390)	0.406 (0.327–0.504)	<0.001	9.0 (7.002–10.998)	0.370 (0.287–0.478)	<0.001
Other	7 (1.4)	1.0 (0.414–1.586)	1.404 (0.661–2.982)	0.377	1.0 (0.414–1.586)	1.595 (0.706–3.604)	0.262
Treatment modalities							
Combined chemoradiotherapy	194 (37.6)	6.0 (4.957–7.043)	Reference		7.0 (5.834–8.166)	Reference	
Chemotherapy	34 (6.6)	3.0 (2.054–3.946)	1.622 (1.115–2.361)	0.012	4.0 (1.972–6.028)	1.693 (1.107–2.589)	0.015
Radiotherapy	100 (19.4)	3.0 (2.149–3.851)	1.434 (1.110–1.852)	0.006	4.0 (2.589–5.411)	1.346 (0.995–1.821)	0.054
No chemotherapy/ radiotherapy	188 (36.4)	1.0 (0.769–1.231)	3.051 (2.450–3.800)	<0.001	1.0 (0.549–1.451)	2.989 (2.316–3.859)	<0.001

2.2. Variables and their definitions

Baseline patient characteristics (age, gender, race), diagnostic information (year of diagnosis, tumor size, AJCC Stage, lymph node metastasis and distant metastases), and treatment (surgery, radiotherapy and/or chemotherapy status) were all collected. Combination therapy were considered as chemotherapy and radiotherapy (combined chemoradiotherapy). Age at diagnosis was grouped as a binary variable: age <55, and age ≥55 years old. Race was categorized as white, black, and others (American Indian/Alaska Native, Asian/Pacific Islander). Given that the median tumor size was 6 cm, we divided the tumor size into three categories: <6 cm, ≥6 cm and unknown. The AJCC Stage (IVA, IVB or IVC) was also included in our analysis. The N stage consisted of N0, N1 and NX, representing no lymph node (LN) metastases, LN metastases and unknown, respectively. The distant metastasis data was classified as no, distant mets without distant LN(s), distant mets with distant LN(s) and other. We further classified surgical extent into three categories based on 'RX Summ-Surg Prim Site (1988+)': no surgery, lobectomy, near/total thyroidectomy, and other. In our study, radiotherapy referred to external beam radiation, so four treatment modalities were assigned based on 'Radiation recode' and 'Chemotherapy recode' in the SEER database: combined chemoradiotherapy (combination therapy), chemotherapy alone, radiotherapy alone, and no chemotherapy/radiotherapy. The primary outcome was overall survival (OS) and cancer-specific survival (CSS). OS was defined as the duration from the data of diagnosis to death from any cause and CSS was defined as the duration from the date of diagnosis until death due to ATC.

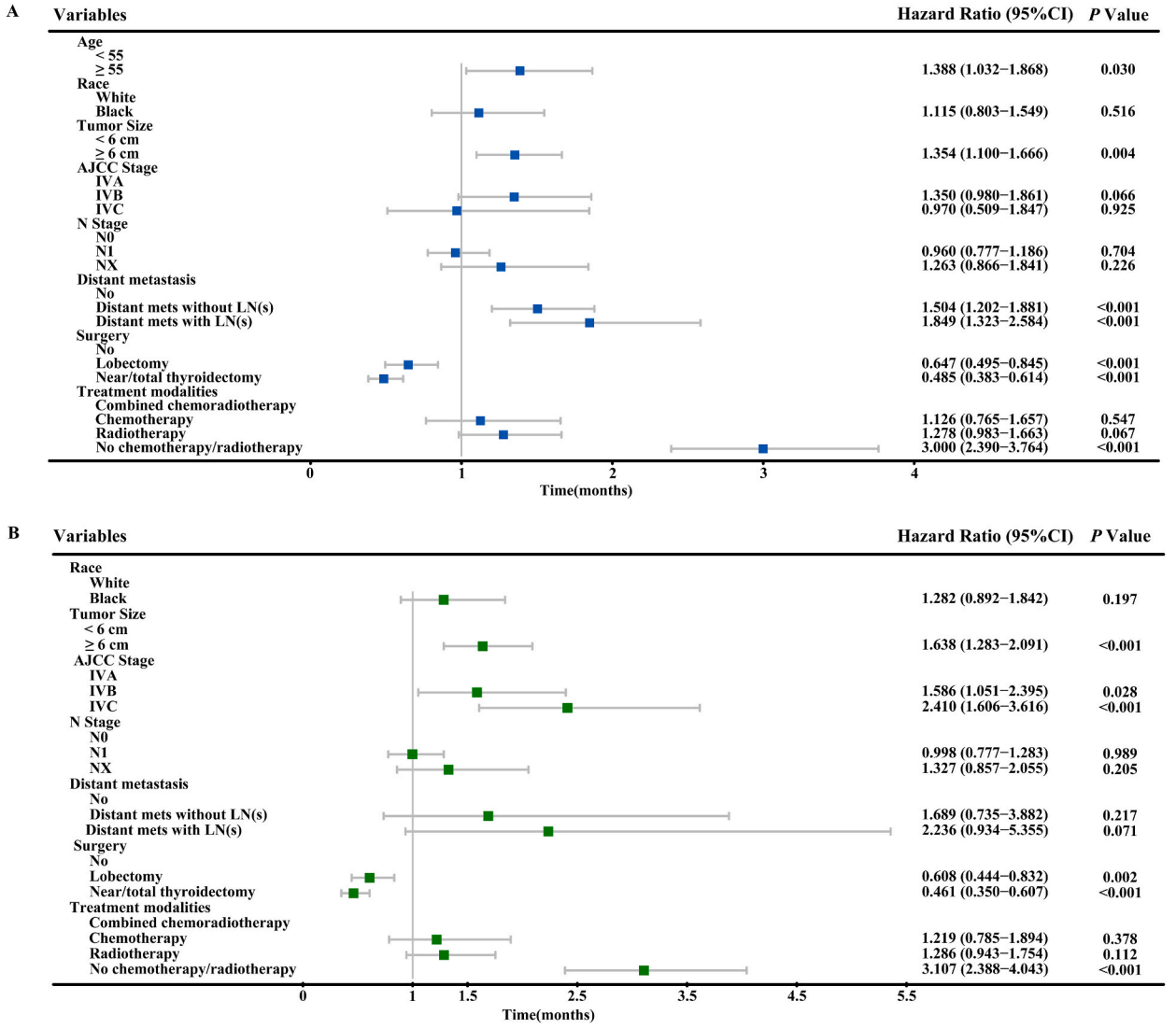

Fig. 2. Multivariable Cox regression analysis for survival among patients with anaplastic thyroid cancer. A. Overall survival. B. Cancer-specific survival. HR, hazard ratio; CI, confidence interval.

2.3. Statistical analysis

The analyses were performed by the SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA) and R 4.0.2 software (R Foundation for Statistical Computing, Vienna, Austria) using some packages. Categorical variables were presented as numbers with percentages. The median OS and CSS were calculated by the Kaplan-Meier method with survival curves compared using the log-rank test. Cox univariate proportional hazard models were used to evaluate the variables associated with clinical outcomes and estimate univariate hazard ratio (HR) and 95 % confidence interval (CI) in patients with ATC. Those significant prognostic factors from the univariate Cox analysis [19] were further performed in the final multivariable Cox model, and the variable selection was performed using a backward LR variable-selection procedure. Note that HRs in the multivariate Cox model can adjust the confounding effects of other covariates. Moreover, the corresponding forest plots were drawn to better represent each prognostic factor associated with OS and CSS in patients with ATC. Survival stratified by chemoradiotherapy was then compared to assess OS and CSS between the treatment subgroups using 1:1 propensity score matching (PSM). Propensity scores were computed based on a logistic regression model adjusting for age, sex, race, tumor size, AJCC Stage, N Stage, distant metastasis, and surgery. The nearest-neighbor matching algorithm without replacement was applied to ensure suitable matches. The caliper was set at 0.02. Categorical characteristics were compared using the Pearson Chi-square test or Fisher's exact test before and after PSM in patients undergoing combination therapy versus chemotherapy or radiation alone. A two-sided P value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 516 patients diagnosed with ATC were included in the analysis whose baseline characteristics are shown in Table 1. We found that the majority of patients (87.6 %) were aged 55 years or older, and their median OS (3 months) was shorter than that (6 months) of patients younger than 55 years. The median tumor size among the patientd was 6 cm. In terms of AJCC staging, 252 patients (48.8 %) were categorized as stage IVC, 202 (39.1 %) as IVB, and 249 did not undergo any surgical intervention (48.3 %). Regarding the chemotherapy/radiotherapy modality, the distribution was as follows: 194 patients (37.6 %) received chemoradiotherapy, 34 (6.6 %) underwent chemotherapy only, 100 (19.4 %) received radiotherapy alone, and 188 (36.4 %) did not undergo any form of chemotherapy or radiotherapy.

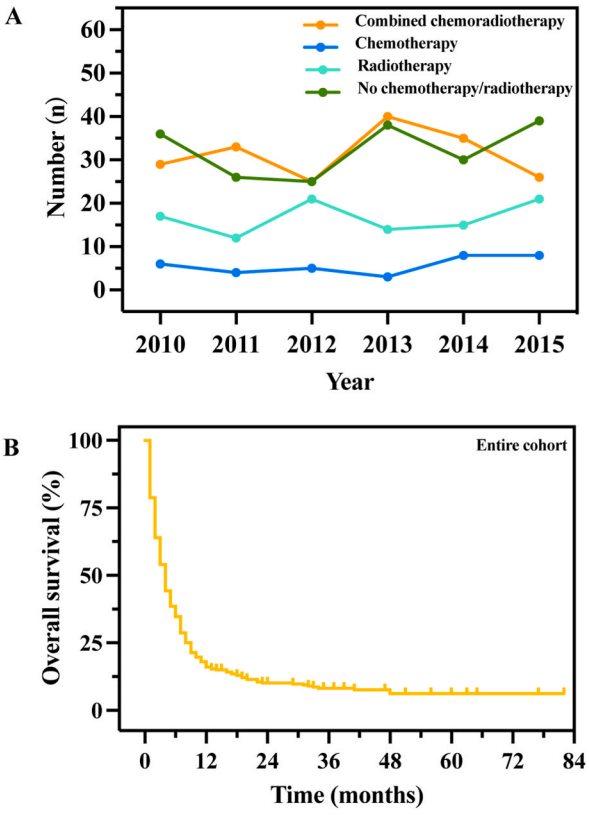

Fig. 3. A. Population distribution of anaplastic thyroid cancer patients receiving four therapeutic modalities from 2010 to 2015. B. Kaplan-Meier survival curve of entire cohort patients with anaplastic thyroid cancer.

3.2. Univariate and multivariate cox analysis for survival

Univariate Cox analysis (Table 1) showed that patients with older age, black race, larger tumor size, higher AJCC stage, lymph node metastases, and distant mets with/without LN(s) were associated with a worse OS. Similarly, patients receiving chemotherapy (HR, 1.622; 95 % CI, 1.115–2.361), radiotherapy (HR, 1.434; 95 % CI, 1.110–1.852) and no chemotherapy/radiotherapy (HR, 3.051; 95 % CI, 2.450–3.800) had a worse prognosis than those undergoing chemoradiotherapy. Conversely, patients receiving lobectomy (HR, 0.590; 95 % CI, 0.459–0.759) and near/total thyroidectomy (HR, 0.406; 95 % CI, 0.327–0.504) had a better prognosis as compared to cases with no surgical operation. Additionally, using univariate analysis we obtained nearly identical results for the variables influencing CSS.

Next, for the significant prognostic variables in the univariate analysis, we performed multivariable Cox regression analysis to investigate the relationship between potential predictors and OS and CSS. As a result, the corresponding forest plots were drawn for OS (Fig. 2A) and CSS (Fig. 2B). A worse OS was linked to the following factors: age ≥55 (HR = 1.388), tumor size ≥6 cm (HR = 1.354), distant mets without LN(s) (vs no, HR = 1.504), distant mets with LN(s) (vs no, HR = 1.894), and no chemotherapy/radiotherapy (vs chemoradiotherapy, HR = 3.000) (all $P < 0.05$). Additionally, larger tumor size (HR = 1.638), higher AJCC stage (IVB vs IVA, HR = 1.586 and IVC vs IVA, HR = 2.410) and lack of chemotherapy/radiotherapy (HR = 3.107) (all $P < 0.05$) were risk factors that significantly reduced CSS. Both better OS and better CSS were associated with lobectomy (OS: aHR = 0.647; CSS: HR = 0.608) and near/total thyroidectomy (OS: HR = 0.485; CSS: HR = 0.608) compared to no surgery (all $P < 0.01$). Intriguingly, chemoradiotherapy did not predict better OS or CSS (all $P > 0.05$).

3.3. Comparison of the different treatment modalities before and after PSM

The population distribution of ATC patients receiving four treatment modalities from 2010 to 2015 is shown in Fig. 3A. The least number of patients received chemotherapy, followed by radiotherapy. However, the overall number of ATC cases receiving four treatment modalities per year was essentially comparable. The median OS for the entire cohort (n = 516) was 3.0 months (95 % CI, 2.58–3.42), and 6- and 12-month OS rates were 29 % (95 % CI, 25.01%–32.88 %) and 13 % (95 % CI, 10.60%–16.58 %), respectively (Fig. 3B). To determine the effect of chemoradiotherapy on survival, the Kaplan-Meier survival estimates stratified by four treatment modalities were analyzed, as depicted in Fig. 4A (for OS) and Fig. 4B (for CSS). The patients receiving chemoradiotherapy experienced the longest median OS (6.0 months; 95 % CI, 4.957–7.043) and CSS (7.0 months; 95 % CI, 5.834–8.166), while cases with no chemotherapy/radiotherapy had the poorest median OS and CSS (both, 1.0 month; 95 % CI, 0.769–1.231 and 0.549–1.451, respectively).

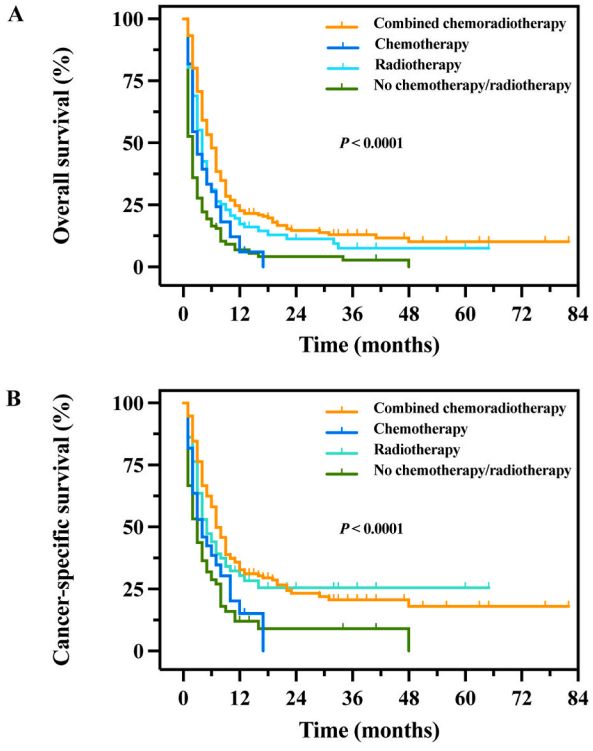

Fig. 4. Kaplan-Meier survival curves for anaplastic thyroid cancer patients receiving four therapeutic modalities. A. Overall survival. B. Cancer-specific survival.

Since the unbalanced baseline characteristics may have a marked impact on survival, to further confirm the conclusion obtained from the multivariate analysis that combined chemoradiotherapy was not superior to chemotherapy or radiotherapy alone, we undertook a 1:1 propensity score matching analysis. The analysis adjusted for age at diagnosis, sex, race, tumor size, AJCC stage, N stage, distant metastasis and surgery procedure, to the utmost to eliminate the baseline variations. For this purpose, 194 patients undergoing chemoradiotherapy and 188 cases with no chemotherapy/radiotherapy were utilized to match 34 chemotherapy patients and 100 radiotherapy patients, respectively. Thus, four well-balanced groups (86, 32, 92, and 30 pairs) were completely matched by propensity score. The comparisons of clinicopathological characteristics between patients receiving combined chemoradiotherapy and chemotherapy alone (Table 2) or radiotherapy (Table 3) before and after PSM are presented. No statistical differences were found after matching. Kaplan-Meier analysis and the log-rank test for OS and CSS were performed in the four matched populations, respectively, as displayed in Fig. 5A–D and Fig. 6A–D. Indeed, compared with patients receiving no chemotherapy/radiotherapy, both OS and CSS were improved for patients undergoing chemotherapy (median OS: 2 months vs 1 month; CSS: 3 months vs 1 month) or radiotherapy (median OS: 3 months vs 1 month; CSS: 4 months vs 2 months) after PSM. However, propensity score-matched Kaplan-Meier curve showed no significant differences in survival outcome between patients undergoing chemoradiotherapy and cases undergoing chemotherapy (median OS: 3 months vs 2 months,$P = 0.382$; median CSS: 5 months vs 4 months, $P = 0.420$) or radiotherapy (median OS: 4 months vs 3 months, $P = 0.065$; median CSS: 6 months vs 4 months, $P = 0.251$), which were roughly consistent with the above results obtained from the multivariate Cox analysis.

Table 2
Comparisons of characteristics between patients receiving combined chemoradiotherapy and chemotherapy alone before and after propensity score matching.

Variables	Treatment modalities Before matching			Treatment modalities After matching		
	Combined chemoradiotherapy (%) (n = 194)	Chemotherapy (%) (n = 34)	P Value	Combined chemoradiotherapy (%) (n = 32)	Chemotherapy (%) (n = 32)	*P* Value
Age at diagnosis (years)			0.545[a]			>0.999[b]
<55	37 (19.1)	5 (14.7)		4 (12.5)	4 (12.5)	
≥55	157 (80.9)	29 (85.3)		28 (87.5)	28 (87.5)	
Sex			0.969[a]			>0.802[a]
Female	92 (47.4)	16 (47.1)		15 (46.9)	16 (50.0)	
Male	102 (52.6)	18 (52.9)		17 (53.1)	16 (50.0)	
Race			0.117[b]			0.755[b]
White	169 (87.1)	26 (76.5)		24 (75.0)	26 (81.3)	
Black	12 (6.2)	2 (5.9)		4 (12.5)	2 (6.3)	
others	13 (6.7)	6 (17.6)		4 (12.5)	4 (12.5)	
Tumor Size(cm)			0.012[a]			0.674[a]
<6	84 (35.6)	10 (29.4)		11 (34.4)	10 (31.3)	
≥6	89 (58.2)	14 (41.2)		15 (46.9)	13 (40.6)	
unknown	21 (6.2)	10 (29.4)		6 (18.8)	9 (28.1)	
AJCC stage			0.005[a]			0.108[b]
IVA	24 (12.4)	7 (20.6)		2 (6.3)	7 (21.9)	
IVB	92 (47.4)	6 (17.6)		12 (37.5)	6 (18.7)	
IVC	78 (40.2)	21 (61.8)		18 (56.3)	19 (59.4)	
N Stage			0.568[a]			0.461[b]
N0	69 (35.6)	9 (26.5)		14 (43.8)	9 (28.1)	
N1	113 (58.2)	23 (67.6)		17 (53.1)	21 (65.6)	
NX	12 (6.2)	2 (5.9)		1 (3.1)	2 (6.3)	
Distant metastasis			0.050[b]			0.967[b]
No	113 (58.2)	12 (35.3)		13 (40.6)	12 (37.5)	
Distant mets without LN(s)	48 (24.7)	11 (32.4)		9 (28.1)	11 (34.4)	
Distant mets with LN(s)	15 (7.7)	5 (14.7)		5 (15.6)	5 (15.6)	
Other	18 (9.3)	6 (17.6)		5 (15.6)	4 (12.5)	
Surgery			0.044[b]			0.580[b]
No	73 (37.6)	18 (52.9)		12 (40.6)	16 (50)	
Lobectomy	37 (19.1)	6 (17.6)		8 (25.0)	6 (18.8)	
Near/total thyroidectomy	84 (43.3)	9 (26.5)		12 (37.5)	9 (28.1)	
Other	0 (0)	1 (2.9)		0 (0)	1 (3.1)	

[a] Pearson Chi-square test.
[b] Fisher's exact test.

Table 3
Comparisons of characteristics between patients receiving combined chemoradiotherapy and radiotherapy alone before and after propensity score matching.

Variables	Treatment modalities Before matching			Treatment modalities After matching		
	Combined chemoradiotherapy(%)(n = 194)	Radiotherapy (%) (n = 100)	P Value	Combined chemoradiotherapy (%) (n = 86)	Radiotherapy (%) (n = 86)	*P* Value
Age at diagnosis (years)			0.076[a]			0.295[a]
<55	37 (19.1)	11 (11.0)		16 (18.6)	11 (13.5)	
≥55	157 (80.9)	89 (89.0)		70 (81.4)	75 (72.5)	
Sex			<0.001[a]			0.522[a]
Female	92 (47.4)	72 (72.0)		54 (62.8)	58 (67.4)	
Male	102 (52.6)	28 (28.0)		32 (37.2)	28 (32.6)	
Race			0.052[a]			0.924[a]
White	169 (87.1)	77 (77.0)		71 (82.6)	69 (80.2)	
Black	12 (6.2)	8 (8.0)		6 (7.0)	7 (8.1)	
Others	13 (6.7)	15 (15.0)		9 (10.5)	10 (9.5)	
Tumor Size(cm)			0.256[a]			0.893[a]
<6	84 (43.3)	50 (50.0)		40 (46.5)	40 (46.5)	
≥6	89 (45.9)	36 (36.0)		35 (40.7)	33 (38.4)	
Unknown	21 (10.8)	14 (14.0)		11 (12.8)	13 (15.4)	
AJCC stage			0.078[a]			0.971[a]
IVA	24 (12.4)	10 (10.0)		11 (12.8)	10 (11.6)	
IVB	92 (47.4)	36 (36.0)		32 (37.2)	32 (37.2)	
IVC	78 (40)	54 (54.0)		43 (50.0)	44 (51.2)	
N Stage			0.691[a]			0.935[a]
N0	69 (35.6)	40 (40.0)		30 (34.9)	31 (36.0)	
N1	113 (58.2)	53 (53.0)		50 (58.1)	48 (55.8)	
NX	12 (6.2)	7 (7.0)		6 (7.0)	7 (8.1)	
Distant metastasis			0.043[a]			0.468[a]
No	113 (58.2)	42 (42.0)		41 (47.7)	40 (46.5)	
Distant mets without LN(s)	48 (24.7)	31 (31.0)		25 (29.1)	26 (30.2)	
Distant mets with LN(s)	15 (7.7)	15 (15.0)		8 (9.3)	13 (15.1)	
Other	18 (9.3)	12 (12.0)		12 (14.0)	7 (8.1)	
Surgery			0.001[b]			0.335[b]
No	73 (37.6)	59 (59.0)		50 (58.1)	45 (52.3)	
Lobectomy	37 (19.1)	13 (13.0)		17 (19.8)	13 (15.1)	
Near/total thyroidectomy	84 (43.3)	27 (27.0)		19 (22.1)	27 (31.4)	
Other	0 (0)	1 (1.0)		0 (0)	1 (1.2)	

[a] Pearson Chi-square test.
[b] Fisher's exact test.

4. Discussion

Anaplastic thyroid cancer (ATC) represents a rare but highly aggressive subtype of thyroid cancer [20]. According to the AJCC 8th Edition, all ATC patients are classified as stage IV (A, B, or C), based on tumor size and extension at presentation [21,22]. Despite the availability of data advocating for mutation-guided personalized targeted therapies and immunotherapeutic approaches in advanced or initially unresectable ATC [23–25], with emerging evidence suggesting potential survival benefits, current guidelines still recommend surgery as the primary treatment modality for ATC patients with stage IVA and IVB [21]. Certainly, in some situations surgical treatment can be followed by additive chemoradiation therapy to improve locoregional control and overall outcome [26,27]. However, given the potential radiation-related adverse effects and increased toxicity caused by chemotherapy, it remains unclear whether combination therapy (chemoradiotherapy) can indeed improve the survival outcome for ATC patients compared to monotherapy [28]. Previous studies have shown that the combination of regression adjustment and propensity score matching has generally superior statistical properties than either method by itself [17,18]. Therefore, using the SEER database platform, our study performed multivariate analysis and propensity score matching after adjusting for the main prognostic factors between radiation treatment and chemotherapy. We discovered that a combination of radio- and chemotherapy versus monotherapy does not improve overall and cancer-specific survival for ATC patients.

Currently, the absence of prospective, multicenter trial regarding the prognostic factors for ATC underscores the significance of population-based cancer registries in investigating the relationship between the predictors and survival outcomes. In this population-based study, potential factors associated with unfavorable overall survival in a multivariate model were older age (≥55 years), larger tumor size (≥6 cm), distant metastasis, no surgical procedure, and no chemotherapy/radiotherapy. These findings were consistent

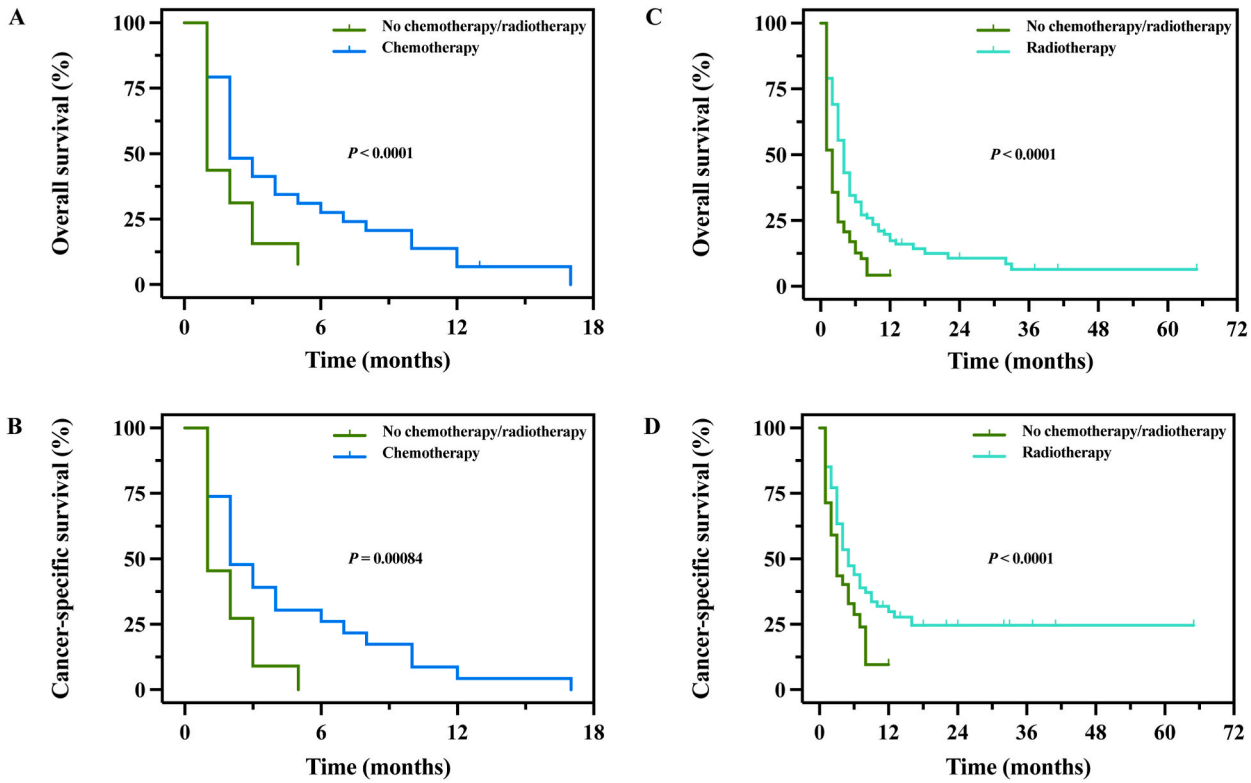

Fig. 5. Kaplan-Meier survival curves between patients with different therapeutic modalities after propensity score matching. A. Overall survival and B. Cancer-specific survival between patients undergoing no chemo/radiotherapy and chemotherapy. C. Overall survival and D. Cancer-specific survival between patients receiving no chemotherapy/radiotherapy and radiotherapy.

with two previously published population-based studies that used the SEER database consisting of 516 and 261 patients, respectively as well as other retrospective studies including 47, 121 and 100 cases [29–33]. Notably, our study also showed that distant metastasis and older age did not independently predict worse cancer-specific survival in the multivariable analysis. The reason, we hypothesize, is that ATC patients presenting with acute airway obstruction are prevalent due to its very aggressive characteristic, and many individuals eventually die from local recurrence and tumor progression rather than advanced age or distant metastases. Some series reported that tracheostomy was required for 40 % of ATC patients and 36 % of patients who died as a result of airway obstruction [34]. Additionally, recent studies suggest that patients with $BRAF^{V600E}$ and MEK mutations may have better survival outcomes when treated with corresponding targeted therapies [35,36], which were unfortunately not included in our study due to the inherent limitations of SEER database.

Some studies reported that approximately 20 % of ATC patients have coexisting differentiated thyroid cancer, recommending a total or near-total thyroidectomy for ATC. If locoregional disease is present, complete resection (R0/R1 resection) is independently associated with improved disease-free survival and overall survival with or without chemoradiotherapy [37– 41]. Consistent with prior research demonstrating that surgical resection is independently associated with longer overall survival, our study revealed that overall survival was better in patients with lobectomy (HR = 0.647), and near/total thyroidectomy (HR = 0.485) than those with no surgery, regardless of other prognostic factors. Similarly, our study also obtained consistent results for cancer-specific survival. Consequently, we advocate for total or near/total thyroidectomy as the optimal surgical approach for ATC patients presenting with locoregional disease.

Although there are no definitive evidence indicating the optimal timing or sequence of radiotherapy and chemotherapy, the prevailing recommendation for the treatment of IVA/IVB ATC involves surgical resection combined with radiotherapy, with or without chemotherapy [21]. Systemic chemotherapy may often be initiated sooner post-surgery than radiotherapy, as it requires less postoperative healing for safe administration. A meta-analysis of 17 retrospective studies involving 1147 patients found that postoperative radiotherapy reduces the risk of death compared with surgery alone [11]. Similarly, a multivariate analysis of a SEER data revealed that the combined use of surgical resection and radiotherapy was identified as an independent predictor of survival [29]. Regarding chemotherapy, a nonrandomized multicenter clinical trial indicated that taxane paclitaxel administered weekly or every 3 weeks resulted in transient disease regression in 53 % of 19 ATC patients [42]. Furthermore, a report conducted by Kawada K et al. showed that docetaxel administered as a single agent every 3 weeks can stabilize disease for some time, and occasionally even produce complete remission [43]. In our population-based study, the propensity scores matched results after adjusting for the differences between the corresponding two groups demonstrated that chemotherapy or radiotherapy alone versus no chemotherapy/radiotherapy

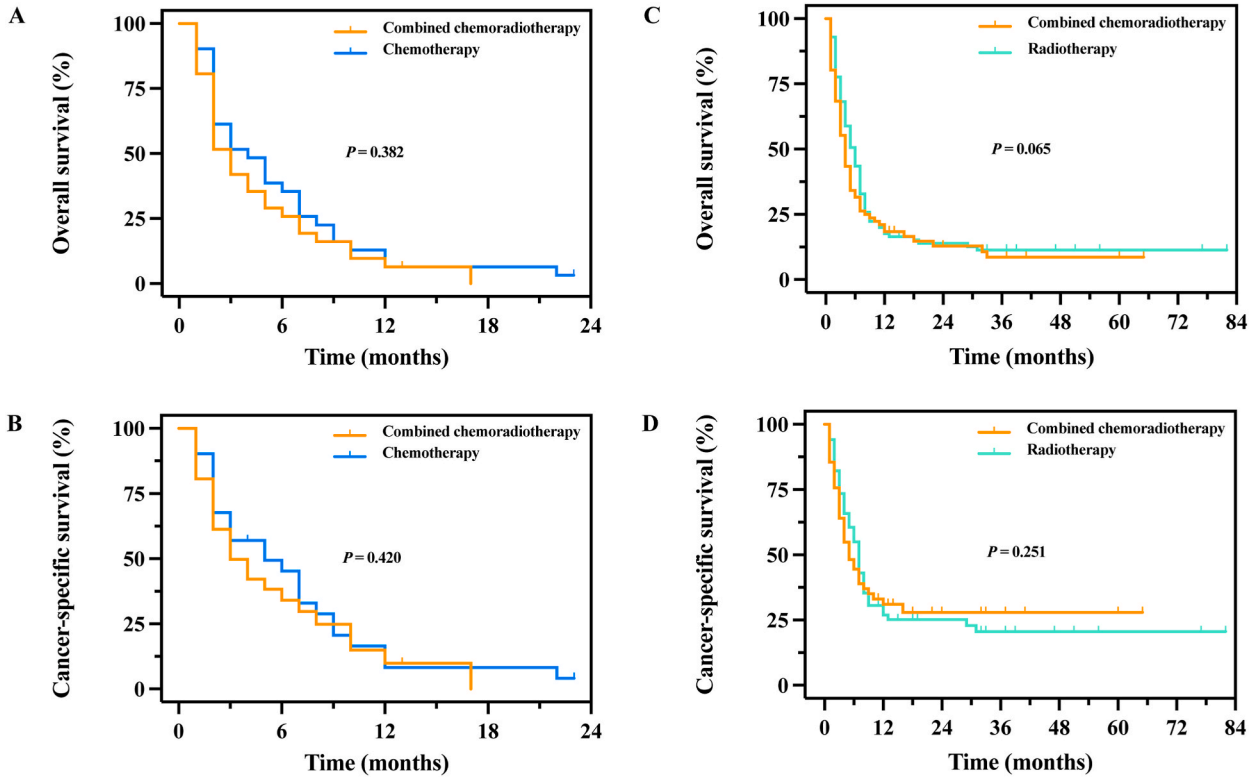

Fig. 6. Kaplan-Meier survival curves between patients with different therapeutic modalities after propensity score matching. A. Overall survival and B. Cancer-specific survival between patients undergoing combined chemoradiotherapy and chemotherapy alone. C. Overall survival and D. Cancer-specific survival between patients receiving combined chemoradiotherapy and radiotherapy alone.

contributes to prolonged OS and CSS in patients with ATC, regardless of surgery or not.

The additional contribution of chemotherapy and radiotherapy to ATC patients has been less well studied and the available data are controversial [44–47]. Concurrent taxane therapy has been proven to have radiosensitizing effects. Sugitani I et al. found that, using the ATC Research Consortium of Japan database of 677 patients, that therapies combining radiation therapy with chemotherapy only significantly improved CSS for AJCC stage IVB patients with ATC who underwent surgery, but did not show additional benefit for stage IVA cases [13]. Recently, mutation-guided individualized targeted therapeutic strategies are now increasing and have obtained a considerably better prognosis than chemotherapy, particularly in advanced or initially unresectable ATC. $BRAF^{V600E}$ mutation is the most prevalent mutation found in ATCs, accounting for 50–70 % of cases [48]. Systemic therapy with BRAF-directed therapy, which can induce prompt and impressive tumor regression in BRAFV600E-mutated IVC and unresectable IVB ATC patients who refuse radiotherapy or have contraindications, can be recommended over other systemic therapies (such as chemotherapy), if available. As for metastatic ATC patients who have exhausted all other therapeutic options including clinical trials, the guideline recommends cytotoxic chemotherapy that includes a taxane and/or an anthracycline or taxane with or without *cis*- or carbo-platin [21]. In our study, utilizing the SEER database encompassing 516 ATC patients, multivariate analysis demonstrated that neither overall survival (OS) nor CSS demonstrated superiority in patients subjected to chemoradiotherapy compared to those receiving chemotherapy or radiotherapy alone, a finding corroborated by propensity score matching. An alternative explanation for the disparities is that estimates from these studies are inconsistent and limited by selection bias (e.g., patients across different stages, different database) and other study design limitations such as the presence of confounders (e.g., exposure to different treatment modalities, participation in clinical trials, or retrospective design, etc).

This SEER database research has some inherent limitations. First, details regarding radiotherapy, such as receipt of high-dose versus low-dose treatment and information about precise regimens of chemotherapy, including the specific drugs and cycles of chemotherapy are not available in the SEER database. Second, the SEER database does not include information about the patient's profession, performance status and comorbidities, as well as novel treatment patterns such as targeted therapy and immunotherapy that have an impact on survival outcomes. Third, SEER does not contain information regarding the time between diagnosis and treatment, which would be required to assess the impact of immortal person-time bias on the current study results.

5. Conclusions

For ATC patients who are not candidates for targeted therapy, although chemotherapy or radiotherapy improves survival

outcomes, the combination of chemotherapy and radiotherapy versus monotherapy, interestingly, does not improve prognosis, implying that more dedicated prospective studies are needed to tailor its treatment management.

Data availability statement

The datasets generated during and/or analyzed during the current study are available at https://seer.cancer.gov/. and also can be obtained from the corresponding author upon any reasonable request.

Ethics approval and consent to participate

As this study is a retrospective analysis of public database (SEER), ethical approval and informed consent for this study was not required.

Funding

The work was supported by the National Natural Science Foundation of China (81801732).

CRediT authorship contribution statement

Wenxin Zhang: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Hui Wang:** Validation, Formal analysis, Data curation, Conceptualization. **Weijian Li:** Validation, Data curation, Conceptualization. **Qiang Jia:** Validation, Supervision, Data curation, Conceptualization. **Ruyi Zhang:** Validation, Software. **Jian Tan:** Writing – review & editing, Validation, Supervision. **Shen Wang:** Visualization, Validation. **Ruiguo Zhang:** Writing – review & editing, Writing – original draft, Validation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

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