

Treatment outcome of anaplastic thyroid cancer patients in Vietnam (period 2014-2022)

N.-V. DANG^{1,2}, N.-C. TIN¹, N.-D. DUC², H.T.V. THANH¹

¹Vietnam National Cancer Hospital, Hanoi, Vietnam

²Hanoi Medical University, Hanoi, Vietnam

Abstract. – OBJECTIVE: Anaplastic thyroid carcinoma (ATC) is an endocrine tumor with low incidence and one of the most aggressive human malignancies. The median survival is only 3-10 months, and the optimal therapeutic approach as well as prognostic factors have not been established. The aim of this study was to evaluate the long-term survival and good prognostic factors of patients with ATC.

PATIENTS AND METHODS: The retrospective study used our institution's single-center database system. 31 patients with histopathological confirmation of anaplastic thyroid cancer from January 2014 to June 2022 were included.

RESULTS: 31 patients with ATC [11 males (35.5%), 20 females (64.5%); average age, 58.7 years] were identified, 32.3% were stage IVA, 32.3% stage IVB, and 35.4% IVC. The median overall survival (OS) of the entire cohort was 6.9 ± 1.45 months. The OS at two years was 12.1%. The female with no cervical lymph node metastasis, undergoing surgery, and tumor size < 6 cm were associated with improved OS. Patients undergoing surgery followed by chemoradiation therapy had the highest median OS (11 ± 1.83 months) and 21.8% of 2-year survival.

CONCLUSIONS: Anaplastic thyroid carcinoma is a highly malignant tumor. Patients receiving surgical resection had better OS than patients without these treatments. The combination of surgery and chemoradiation could improve OS.

Key Words:

Anaplastic thyroid cancer (ATC), Multimodal treatment, Overall survival, Surgery, Chemoradiation.

thyroid cancer, it comprises more than 50% of all deaths caused by thyroid malignancy^{3,4}. The median overall survival was estimated at six months or less, with a one-year survival rate of around 20%^{5,6}.

ATC is currently treated with surgery, chemotherapy, radiotherapy and/or targeted therapy. Surgery is the most effective treatment for improving prognosis; however, most cases are inoperable at presentation due to the extent of local disease or distant metastasis^{7,8}. Radiation therapy and chemotherapy are generally used as a postoperative treatment or definitive therapy for unresectable diseases. Some studies^{9,10} demonstrated promising results in the treatment of ATC with targeted therapy and immunotherapy. Despite multimodality treatment, ATC outcomes are poor, with the median overall survival (OS) of patients being 0.5 to 6 months worldwide.

Optimal ATC treatment is questionable due to the lack of randomized trials. Previous scholars^{11,12} showed that the use of targeted therapy, immunotherapy, surgery, and radiation therapy was associated with improved overall survival in patients with anaplastic thyroid carcinoma. Retrospective studies^{12,13} identified some prognostic factors, such as age, gender, presence of acute symptoms, tumor size, multicentricity, metastatic spread, white blood cell level, blood platelet level, and serum albumin level, that influenced the survival of patients with ATC. Few studies^{11,12} have evaluated outcomes for the treatment of ATC. Here, we conducted this retrospective study to analyze the OS and determine the factor's association with long-term survival.

Introduction

Thyroid cancer is the most common type of endocrine cancer worldwide. Most thyroid cancers, especially papillary thyroid cancer, which accounts for nearly 90% of all thyroid malignant tumors, have an excellent prognosis^{1,2}. Although anaplastic thyroid carcinoma (ATC) accounts for 1-2% of all

Patients and Methods

Patient Data Collection

This retrospective study was independently reviewed and approved by the Institutional Review Board of Hanoi Medical University. We evaluated 31 patients with pathologically con-

firmed anaplastic thyroid cancer at our hospital from January 2014 to June 2022. The American Joint Committee on Cancer (AJCC) staging system (8th edition)¹⁴ was used to determine tumor staging. Patient demographic characteristics, sex, age, comorbidity, treatment modalities (surgery, chemotherapy, radiation therapy, immunotherapy), results and dates of all imaging studies, status at last follow-up and overall survival were collected.

Treatment and Survival

Treatment modalities included surgery (total thyroidectomy and bilateral neck dissection), chemotherapy, and radiotherapy. The patient would receive one of these treatments alone or in combination with two or more options.

Surgery: The surgical intervention was total thyroidectomy with bilateral neck dissection.

Radiation therapy: All patients underwent immobilization with a thermoplastic head-neck or, more recently, head-neck-shoulder mask to ensure daily reproducibility of the radiotherapy fields. All patients received radiation treatment once a day, five times a week. For chemoradiation, the total dose was up to 70 Gy; for postoperative radiation or chemoradiation, the total dose was up to 66-70 Gy for positive margin and 60 Gy for negative margin.

Systemic therapy: Patients were treated with varying types of systemic agents including doxorubicin, cisplatin, paclitaxel, docetaxel. Doxorubicin doses were 20 mg/m² weekly with or without radiation therapy. All treatment regimens were approved by our hospital's Multidisciplinary Tumor Board.

The OS was measured from the date of pathologic confirmation of ATC to the date of death, with patients censored at the date of the last follow-up.

Statistical Analysis

The two-tailed Pearson χ^2 test (or Fisher's exact test when categorical variable values were ≤ 5) was used to analyze categorical variables. Survival was estimated using the Kaplan-Meier method, and any difference in survival was evaluated using the stratified log-rank test. Multivariable analysis with the Cox proportional hazards model was utilized to estimate the simultaneous effects of prognostic factors on survival. Statistical significance was defined for $p < 0.05$. All analyses were performed using IBM SPSS v. 27 (IBM Corp., Armonk, NY, USA).

Results

Demographic Characteristics

From January 2014 to June 2022, a total of 31 patients with pathologically diagnosed ATC were included. Eleven patients were males (64.5%), and 20 were females (35.5%), with a female-to-male ratio of 1.8:1. The average age was 58.7 years, with most of the patients over 60 years (61.3%) (Table I).

The most frequent tumor stage was IVC (35.6%), with the remaining stage distribution as follows: 32.2% stage IVA and 32.2% stage IVB. At the time of presentation, enlarging neck mass was the most common symptom (93.5%); the others include hoarseness (35.5%), dyspnea (19.4%), and dysphagia (54.8%). The percentage of cervical lymph nodes was 64.5%; 11 patients (35.4%) had distant metastasis, and the most common site was the lung. A total of 23 patients (74.2%) underwent surgery (total thyroidectomy and bilateral neck dissection), local extrathyroidal invasion was 47.8% in which the tumor invaded to muscle was 35.4%, trachea (25.8%) and esophagus (6.4%). Most of the patients received multimodality therapy, including 18 (58%) with surgery and chemoradiotherapy, 5 (16.1%) with surgery and radiotherapy, 5 (16.1%) with chemoradiotherapy; only two patients were treated with monotherapy (surgery alone), and three patients received palliative treatment (Table I).

Overall Survival

The median overall survival (OS) was 6.9 months, ranging from 1.13 to 41.7 months. The six-month, 1-year, and 2-year OS for the entire cohort was 64%, 24.2%, and 12.1%, respectively. The median OS according to age group was 7.86 ± 2.36 and 6.75 ± 0.8 months for patients younger than 60 and patients over 60 years, respectively ($p > 0.05$). In contrast, there was a significant difference ($p < 0.01$, Table II) in survival between males (median OS 2.6 months) and females (10 months). Similarly, patients with stage IVA had significantly longer OS (13.5 months) than those with stage IVB (6 months) or IVC (3.6 months) ($p < 0.01$).

In our study, 23 patients performed surgery, which all received total thyroidectomy and bilateral neck dissection. The median OS for patients receiving surgery was nine months compared with patients who did not undergo surgery, which was 2.16 months ($p < 0.01$). The results

Table I. General characteristics, tumor stage, and treatment.

Characteristics	Number of patients (n)	%
Sex		
Male	11	64.5
Female	20	35.5
Age		
< 60	12	38.7
≥ 60	19	61.3
Symptoms at presentation		
Enlarging neck mass (thyroid mass or lymph node)	29	93.5
Hoarseness	11	35.5
Dyspnea	6	19.4
Dysphagia	17	54.8
Tumor size		
< 6 cm	12	38.7
≥ 6 cm	19	61.3
Stage (AJCC 2017)		
IVA	10	32.2
IVB	10	32.2
IVC	11	35.6
Metastasis		
Adjacent structures (intraoperative evaluation) (n = 23)		
Muscle	11	47.8
Trachea	8	34.7
Esophagus	2	8.6
Cervical vessels	5	21.7
Cervical nerves	8	8.6
Cervical lymph nodes		
Yes	20	64.5
No	11	35.5
Distant metastases		
No	20	64.6
Yes	11	35.4
Pulmonary	11	35.4
Bone	3	9.6
Treatment		
Surgery alone	2	6.5
Surgery + radiotherapy	3	9.7
Chemotherapy + radiotherapy	5	16.1
Surgery + chemoradiotherapy	18	58
Palliative treatment	3	9.7

showed that patients undergoing surgery followed by chemoradiation therapy had the highest median OS (11 ± 1.83) compared with other treatment modalities ($p < 0.01$) (Table II).

Discussion

ATC has long been regarded as a highly malignant and very short-lived disease^{3,6}. ATC was reported to be more common in women than in men. According to the data from the Surveillance, Epidemiology, and End Results database¹⁵ from 1973 to 2014, among 1,527 patients with a diagnosis of ATC, 959 (62.8%) patients were women, and 568 (37.2%) were men, and the mean age was 70.5 years. A similar result was reported in our study, with the ratio of females and males being 1.8:1. ATC was found to occur more frequently in patients over 60 years, accounting for 61.3%, which is consistent with previous reports^{2,16}. Patients with ATC usually present with a rapidly grow-

ing and invasive neck mass and regional cervical lymph node involvement. In addition, half of the patients have distant metastasis at the time of diagnosis. In our study, the evidence of lymph node metastasis was based on postoperative pathology or core needle biopsy. Among the 31 patients with ATC, 20 patients (64.5%) had cervical lymph node metastasis, and 11 patients had distant metastasis. All 11 patients had distant metastasis in the lung. This is consistent with the study of Carcangiu et al¹⁷, which included 70 patients with ATC and showed that the lung is the most prominent site of metastasis. The tendency of local invasiveness of ATC may lead to compressive symptoms such as dysphagia, dyspnoea, hoarseness, and pain. In the current study, the percentage of patients who had dysphagia, dyspnoea, and hoarseness was 54.8%, 19.4%, and 35.5%, respectively. This was similar to the result of a retrospective study¹⁸ in which most of the patients had compressive symptoms (82.6%) on diagnosis.

Management of ATC remains challenging

Table II. Multivariate analysis of survival time.

Prognostic factors	Number	Univariate analysis	
		Median OS	p-value
Sex			
Male (11)	11	2.6 ± 0.7	< 0.01
Female (20)	20	10 ± 1	
Age			
< 60 (12)	12	7.86 ± 2.36	> 0.05
≥ 60 (19)	19	6.75 ± 0.8	
Tumor size			
< 6 cm (12)	12	11 ± 2.8	< 0.01
≥ 6 cm (19)	19	6 ± 1.7	
Stage			
IVA	10	13.5 ± 3.72	< 0.01
IVB	10	6 ± 1.22	
IVC	11	3.6 ± 1.46	
Treatment			
Surgery	23	9 ± 2.2	< 0.01
Non-surgery	8	2.16 ± 0.63	
Treatment types			
Surgery alone	2	2.55 ± 0	< 0.01
Surgery + radiotherapy	3	6 ± 2.99	
Chemotherapy + radiotherapy	5	2.17 ± 0.46	
Surgery + chemoradiotherapy	18	11 ± 1.83	

OS: overall survival.

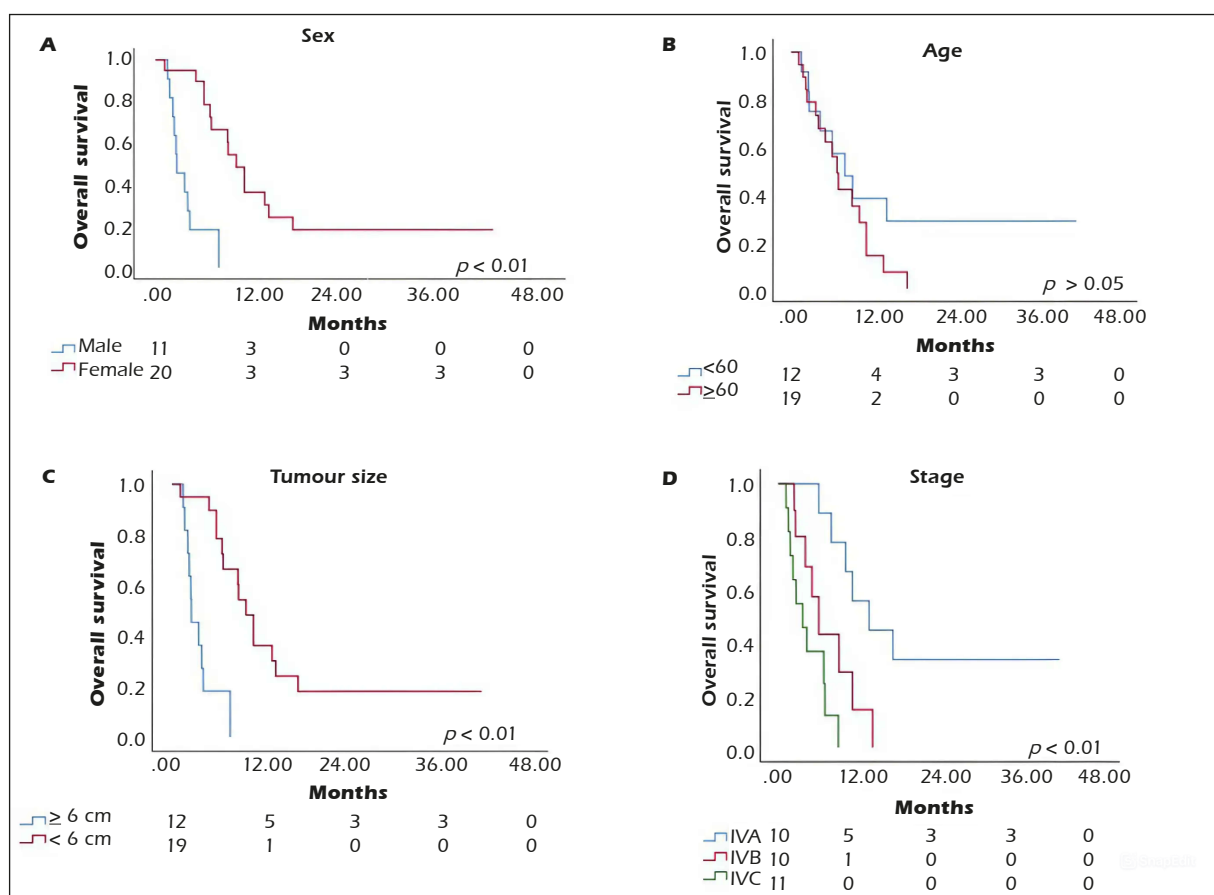


Figure 1. Overall survival. **A**, By sex. **B**, Differences in survival between age > 60 years and age < 60 years. **C**, By tumor size. **D**, Differences in survival among different stages.

due to the aggressive histology, the high rate of locoregional invasion, and the presence of distant metastasis. Of the 31 patients included in this study, the median OS for the entire cohort was 6.9 months. The prognosis was worse in patients over 60 years, but there was no statistical difference (Figure 1). Our data indicated that the median OS was higher in females than males ($p < 0.01$) (Figure 1), which is consistent with a report by Rao et al¹⁹, who showed that men were three times more likely to die from ATC than women. Several previous studies^{11,20,21} have indicated that surgical resection was associated with improved outcomes in ATC patients. In this current study, 23 patients with resectable primary tumors received radical surgery (total thyroidectomy and bilateral neck dissection) and showed significantly longer OS (9 months) compared with 2.16 months of the inoperable group ($p < 0.01$). The role of surgery was profoundly analyzed by Haymart et al²², with 1,072 patients with ATC having surgery compared with 1,013

patients not having surgery. The results showed that 686 patients who received total thyroidectomy had a median survival of 5.8 months, 386 patients who underwent lobectomy had a median survival reduced to 4.5 months, and the median survival was only 2.3 months for patients without surgery. Both the National Comprehensive Cancer Network (NCCN) guidelines and the American Thyroid Association (ATA) recommend total thyroidectomy surgery as standard treatment for resectable primary tumors in ATC²³. The theoretical basis for this is that ATC usually has multifocal lesions and the coexistence of well-differentiated thyroid cancer in which total thyroidectomy offers a higher chance of radical treatment, facilitating further treatment, along with radioactive iodine accompanying differentiated thyroid cancer. A tumor size of less than 6 cm was associated with a good prognosis (median OS: 11 months) (Figure 1). This may be explained by the fact that early detection increases the chance of performing radical treatment.

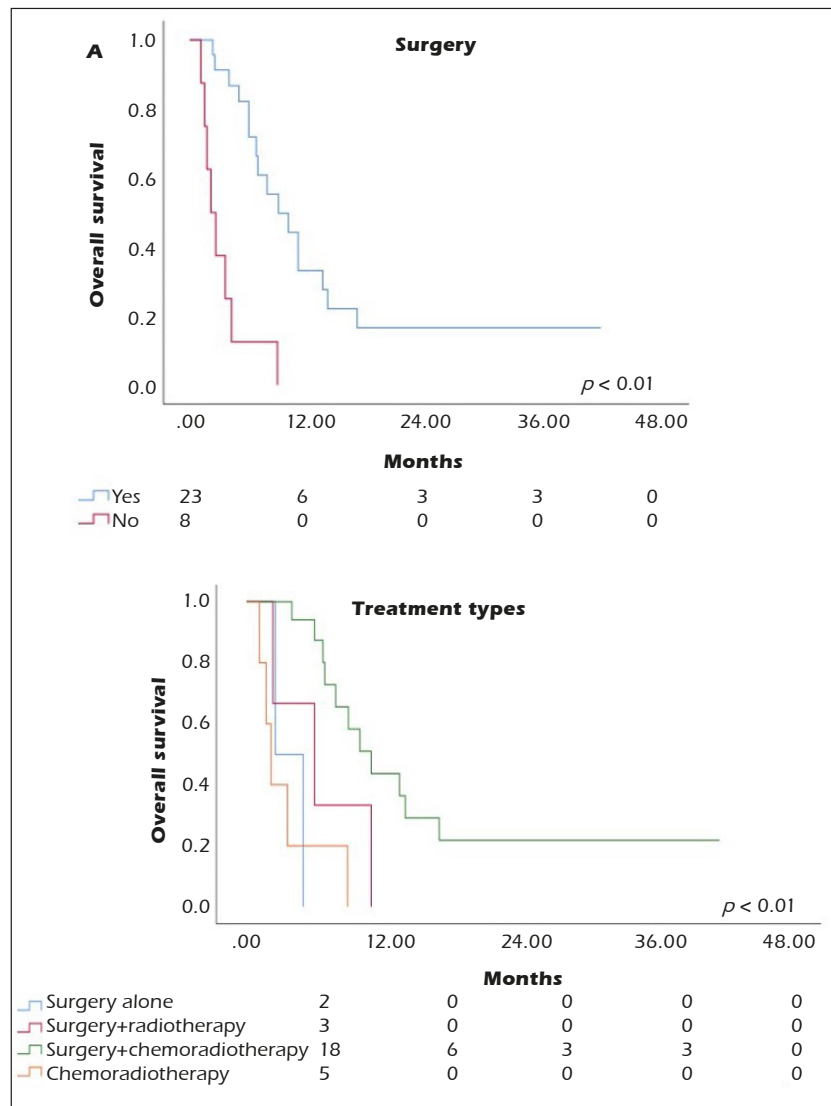


Figure 2. Overall survival. **A,** Patients who underwent surgery vs. no surgery. **B,** Comparative OS in patients by treatment types.

In our study, 67.7% of the patients underwent surgery and received multimodal therapy, including chemotherapy with doxorubicin 20 mg/m² weekly and radiotherapy with a dose of 60 Gy for R0 and 60 to 70 Gy for R1-2 margin. The benefits of postoperative radiation therapy for ATC are recognized by most experts and scholars²⁴. A study²⁰ with 28 patients showed that anaplastic thyroid cancer patients receiving external beam radiation therapy (EBRT) to the thyroid area/neck and/or surgical resection had better OS than patients without these therapies. The optimal radiation dosing and fractionation plan remains unclear. Some previous studies^{25,26} argued against hyperfractionation due to the

absence of survival benefits and increased incidence of toxicities, while others showed that hyperfractionation (46 Gy in 29 fractions) after observing improved local control. A critical review by Sherman et al²⁷ concluded that a median radiotherapy dose of 57.6 Gy and weekly doxorubicin 10 mg/m² was associated with one-year outcomes for locoregional progression-free survival at 45% and overall survival at 28%²⁷. Another retrospective study²⁸ with 104 patients with histologically confirmed ATC demonstrated that the median OS for patients receiving ≥ 60 Gy was 10.6 months compared with 3.6 months among patients receiving < 60 Gy and statistically significant differences in the 1-year

OS between the two groups (47.9% vs. 17.4%, $p < 0.001$). The importance of radiation is further demonstrated by a recent National Cancer Database (NCDB) analysis²⁹ of over 1,200 patients with unresected anaplastic thyroid cancer, which found a positive radiation dose-survival correlation among the entire study cohort. The median survival was 1.31 ± 0.08 months for those who did not receive neck radiotherapy (RT), 1.97 ± 0.127 months for the group that received from 1 to 44.9 Gy, 4.24 ± 0.355 months for the group that received from 45 to 59.9 Gy, and 6.77 ± 0.391 for those who received from 60 to 75 Gy. These data support our findings that high-dose radiation is associated with improved outcomes in the context of multimodal therapy.

While surgery and radiation provide improved local control of anaplastic thyroid cancer, the aggressive nature of the disease commonly results in metastatic spread and death. ATC is characterized by a higher mutation burden with an increased rate of alterations in tumor suppressors (TP53), *PI3K/AKT* pathway genes, and the telomerase reverse transcriptase (*TERT*) promoter, which is poorly responsive to chemotherapy. Targeted therapy and immunotherapy may bring new opportunities for systemic treatment options. It is estimated³⁰⁻³³ that between 20% and 50% of ATCs harbor activating B-RAF kinase (BRAF) V600 mutations with unknown prognostic significance. A clinical trial³⁴ demonstrated the survival improvement with a combination of dabrafenib and trametinib therapy in BRAF V600-mutant anaplastic thyroid cancer patients, which led to the first US Food and Drug Administration (FDA)-approved drug combination for ATC. A retrospective study³⁵ demonstrated the effectiveness of the combination of lenvatinib and pembrolizumab for ATC patients, which showed complete remission in 66% of patients (4/6) and median progression-free survival of 16.5 months. Several prospective trials³⁶⁻³⁸ have begun studying the role of tyrosine kinase inhibitors, such as axitinib, sorafenib, imatinib, and lenvatinib, and have shown promising results. A recent case series³⁹ showed the feasibility of complete resection and locoregional disease control with symptom amelioration for patients with BRAF V600E-variant ATC treated with dabrafenib and trametinib followed by surgical resection. Further study of mutation profiles for ATC may lead to the development of more targeted therapies for selected patient populations.

Limitations

This study has several limitations. First, it has a retrospective, observational design, and the results were dependent on the completeness and accuracy of the medical records used. Second, it has a small number of patients. Another limitation is the lack of genetic testing, and novel systemic therapy (targeted and immunotherapy) was not used in this study.

Conclusions

In conclusion, ATC is one of the most malignant diseases. Our study in a single institution with anaplastic thyroid cancer identifies several factors associated with good outcomes. Although the prognosis remains poor regardless of treatment, patients with ATC who underwent multimodality treatment, including surgery, chemotherapy, and radiotherapy, would improve the OS.

Conflict of Interest

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval

The study was reviewed and approved by the Ethics Committee of Hanoi Medical University, Vietnam, with number: 5622/QD-DHYHN on February 5th, 2021.

Informed Consent

Written informed consent was obtained from the individual(s) for their data to be used in this study.

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Authors' Contributions

Conception, design and study supervision: N.V.D., H.T.V.T.; development of methodology: N.V.D., H.T.V.T., N.D.D.; performing research and analyzing data: N.D.D., N.C.T.; acquisition of data: N.V.D., N.C.T., N.D.D.; writing review, and/or revision of the manuscript: N.V.D., N.D.D. All authors have read and agreed to the published version of the manuscript.

ORCID ID

Nguyen Van Dang: 0000-0002-3370-478X
Nguyen Dinh Duc: 0009-0004-6439-3066

Data Availability

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

AI Disclosure

The authors declare that no use of AI and AI-assisted technologies in the writing process.

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