Original Article

Efficacy evaluation and influencing factor analysis of postoperative ^{131}I for the treatment of primary hyperthyroidism combined with differentiated thyroid cancer (DTC)—a retrospective cohort study

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Background: ^{131}I treatment is one of the important methods of comprehensive postoperative treatment for patients with hyperthyroidism complicated with differentiated thyroid cancer (DTC). Early identification of patients with poor treatment efficacy of ^{131}I is particularly important. Current studies mainly focus on the relationship between hyperthyroidism and the occurrence and development of DTC, and there are few studies on the factors affecting the curative effect. The purpose of this study was to find the influencing factors of efficacy evaluation and provide evidence for early identification of patients with poor efficacy in DTC combined with primary hyperthyroidism patients.

Methods: This was a retrospective analysis of DTC patients with primary hyperthyroidism who received ^{131}I treatment in our department from 2012 to 2021. Follow-up intervals were 3 months within 1 year, 6 months within 1 to 2 years, and annual follow-up thereafter, the median follow-up time was 12.0 (3.0, 24.0) months. Serological examination and imaging examination were used to evaluate the efficacy. Patients were classified into an excellent response (ER) group and a non-ER group based on treatment response more than 6 months after ^{131}I treatment. Univariate analysis and multivariate logistic regression analysis were performed on the basic clinical characteristics, pathological characteristics and curative effect of the patients, in order to find independent risk factors affecting the curative effect.

Results: Eighty-nine patients were mostly female (80.9%), the average age was 43.47±11.88 years old, and tumor size was 1.2 (0.75, 1.80) cm, 56 patients (62.9%) in the ER group. psTg [odds ratio (OR): 1.325; 95% confidence interval (CI): 1.135–1.547; P<0.001], maximum tumor diameter (OR: 2.428; 95% CI: 1.392–4.235; P=0.002) and pathology-confirmed combined HT (OR: 8.669; 95% CI: 1.877–40.038; P=0.006) were independent risk factors for predicting ER.

Conclusions: Our findings demonstrate that most hyperthyroidism combined with DTC patients could get favorable clinical outcomes from ^{131}I treatment. The tumor diameter, pathology-confirmed diagnosis of combined HT, and psTg level can be used to identify patients who can get ER by the effect of ^{131}I in hyperthyroidism combined with DTC at an early stage.

Keywords: Hyperthyroidism; thyroid neoplasms; iodine radioisotopes; therapeutic evaluation; thyroglobulin

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Introduction

Thyroid cancer (TC) is the most common endocrine tumor, and its incidence is increasing year by year. According to the Global Cancer Statistics 2020, among cancers, the incidence of TC ranks ninth, with more than 95% being differentiated thyroid cancer (DTC) (1). Serum thyroid stimulating hormone (TSH) stimulates TC cell growth. Previous study has shown that every 1 mU/L increase in TSH increases the risk of DTC by 14% (2). DTC combined with primary hyperthyroidism occurs in a state of serum TSH suppression, with a low incidence. Surgical treatment is the preferred treatment, and ^{131}I treatment is one of the main measures of postoperative comprehensive treatment. The vast majority of patients can achieve satisfactory curative effect after ^{131}I treatment, but some patients have poor curative effect and may be refractory to iodine treatment or even die. Therefore, it is particularly important to identify these patients with poor curative effect at an early stage. Most current studies have analyzed the clinicopathological features of patients with hyperthyroidism complicated with DTC and the relationship between the occurrence and development of hyperthyroidism and DTC, and few studies have affected the therapeutic effect of ^{131}I in these patients (3). By analyzing the relationship between dynamic efficacy evaluation and clinicopathological features after ^{131}I treatment in patients with hyperthyroidism complicated with DTC, this study is expected to find the influencing factors of efficacy evaluation and provide evidence for early identification of patients with poor efficacy and clinical diagnosis and treatment plan. We present the following article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-749/rc).

Highlight box

Key findings

- Tumor diameter, pathology-confirmed diagnosis of combined HT, and psTg level are independent factors influencing the therapeutic effect of ^{131}I and more likely to obtain ER.

What is known and what is new?

- Hyperthyroidism is related to the occurrence and development of DTC, and ^{131}I therapy is an important auxiliary means of postoperative treatment.
- The efficacy of ^{131}I therapy in patients with hyperthyroidism combined with DTC is related to clinicopathological features, such as tumor diameter, psTg level and pathology-confirmed diagnosis of combined HT.

What is the implication, and what should change now?

- Using these factors can help to identify patients with poor efficacy of hyperthyroidism complicated with differentiated thyroid cancer, Further search for more effective factors to predict curative effect, early detection of patients with poor curative effect.

Methods

Subjects

Eighty-nine primary DTC patients with primary hyperthyroidism who underwent ^{131}I treatment in the Affiliated Hospital of Qingdao University from January 2012 to May 2021 were retrospectively analyzed. The inclusion criteria were as follows: (I) total thyroidectomy + cervical lymph node dissection, with a postoperative pathological diagnosis of DTC; (II) all patients with hyperthyroidism and DTC diagnosed with primary hyperthyroidism before surgery (including Graves' hyperthyroidism, toxic adenoma and toxic nodular goiter) (4); (III) serum thyroglobulin antibody (TgAb) negative (TgAb ≤115 kU/L); (IV) met the criteria for medium- and high-risk stratification of recurrence in the *2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer* (5); and (V) ≥6 months of follow-up. The exclusion criteria were as follows: (I) combined with a history of other malignant tumors or major diseases; and (II) incomplete clinicopathological and follow-up data. The study was conducted in accordance with the Declaration of Helsinki (revised 2013). This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (No. QYFY WZLL 27241). Informed consent was not required as this was a retrospective study.

Inspection method

All patients underwent total thyroidectomy + cervical lymph node dissection. Postoperative pathological examination was performed routinely. Patients with hyperthyroidism were treated with oral drugs (thioureas and imidazoles) or compound iodine solution to control the symptoms of hyperthyroidism before surgery. ^{131}I treatment was performed under TSH stimulation (TSH >30 mU/L) 3 to 4 weeks after surgery. The postoperative staging and pretreatment ^{131}I assessment of patients were based on the *2015 American Thyroid Association Management Guidelines*

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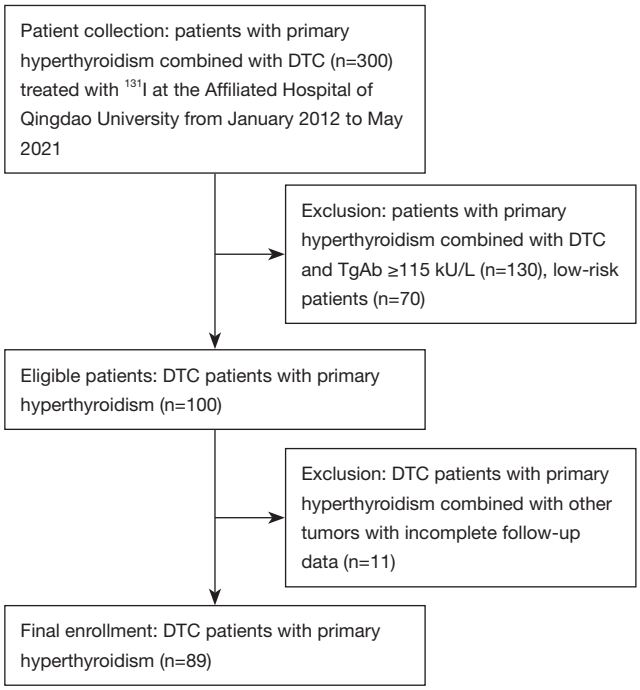

Figure 1 Flowchart. DTC, differentiated thyroid cancer; TgAb, thyroglobulin antibody.

for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (5). Thyroid function, preablative stimulated thyroglobulin (psTg), and TgAb levels were measured, and L-T4 inhibitory treatment was administered 48–72 hours after ^{131}I treatment. General population data such as sex, age at diagnosis, etc., were collected. Maximum tumor diameter, lymph node metastasis, capsule invasion, and pathology-confirmed combined Hashimoto's thyroiditis (HT) were obtained by routine pathologic reports. Tumor recurrence was observed during follow-up after treatment. Follow-ups were 3 months in 1 year, 6 months in 1 to 2 years, and once a year thereafter. Patients were followed up mainly through outpatient department and electronic medical records. Serum TSH, Tg and TgAb levels were measured regularly, and neck ultrasonography, diagnostic ^{131}I whole-body scans (Dx-WBS), and single-photon emission computed tomography/computerized tomography (SPECT/CT) were performed for tomographic fusion imaging. If structural disease was present, a pathological examination was performed to determine whether local recurrence and/or distant metastasis were present. The evaluation of efficacy was based on follow-up results 6–12 months after the last ^{131}I treatment. Using the classification criteria in the *2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer* (5), 4 categories were used to classify response to treatment: excellent response (ER), biochemical incomplete response (BIR), structural incomplete response (SIR) and indeterminate response (IDR). Patients were further divided into an ER group and non-ER group (which included BIR, SIR, and IDR) on the basis of the treatment response. The factors that influenced the efficacy of treatment in patients with DTC in the hyperthyroid group were determined. ER was defined as negative serum TgAb level, inhibitory Tg <0.2 mg/L or irritant Tg <1.0 mg/L, and negative on imaging The start time of follow-up was 1 month after ^{131}I treatment, and the end time was tumor recurrence, patient death or the end date of follow-up in this study. Tumor recurrence refers to the presence of DTC tumor or lymph node metastasis confirmed by cervical ultrasound, Dx-WBS, or pathological examination. Serum Tg and TgAb concentrations were determined by electrochemiluminescence immunoassay (Roche, Switzerland, E170), with a detection range of 0.100–500.000 μg/L and 10–4,000 kU/L (the normal reference ranges are 1.40–78.00 μg/L and 0–115 kU/L). TSH concentration was determined by chemiluminescence immunoassay (Bayer, Germany, ADVLA CENTAVRXP), with a detection range of 0.04–100.00 mU/L (normal reference range is 0.27–4.20 mU/L).

Statistical methods

The data were analyzed using IBM SPSS 26.0 software. Quantitative data with a normal distribution are presented as the mean ± standard deviation ($\bar{x}$±s). Data with a nonnormal distribution are presented as the median M (P25, P75). Comparisons between 2 groups were performed using the 2 independent samples *t*-test or Mann-Whitney U test. Count data are presented as the frequency (rate). Differences between 2 groups were compared using the χ^2 test or Fisher's exact test. Factors significant in univariate analysis were included in multivariate logistic regression analysis to find independent influencing factors affecting treatment response. A two-sided P value <0.05 was considered a statistically significant difference. The test level was α =0.05.

Results

A total of 89 patients were included in this study (*Figure 1*). All patients had no distant metastasis. The median dose of

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^{131}I in the first treatment was 3.70 (3.70, 4.44) GBq, and the first treatment was adjuvant therapy. The duration of hyperthyroidism in the 89 patients (the time interval between the diagnosis of hyperthyroidism and the diagnosis of DTC) ranged from 1 to 264 months, and the median follow-up time was 12.0 (3.0, 24.0) months. Among the 89 patients, 17 were male (19.1%), and 72 (80.9%) were female, for a male to female ratio of approximately 1:4; the age range was 23.0–69.0 years, with an average age of 43.47±11.88 years; 56 patients (62.9%) were included in the ER group, and 33 patients (37.1%) were included in the non-ER group (10 BIR, 14 SIR, and 9 IDR). (*Table 1*). Hyperthyroidism with DTC is more common in women, the average age was 43.47±11.88 years old, and tumor size was 1.2 (0.75, 1.80) cm. They were more prone to lymph node metastasis, mainly in the central region. The overall efficacy of ^{131}I treatment was better, 62.9% (56/89) could reach ER.

Comparison of clinicopathological characteristics of DTC patients in the hyperthyroidism group with different treatment efficacies

Comparisons of the ER group and non-ER group indicated that the ER group had more women (P=0.009, χ^2=6.88), a higher incidence of pathology-confirmed combined HT (P<0.001, χ^2=16.72), smaller tumor diameter (P=0.008, U=1,234.50), higher preoperative TSH levels (P=0.013, U=631.00), lower psTg levels (P<0.001, U=1,585.50), lower first ^{131}I dose (U=11,140.00, P=0.031), earlier T stage (χ^2=14.84, P=0.001), and more preoperative pharmacological control of hyperthyroid symptoms (χ^2=10.62, P=0.005). The differences in the above factors were statistically significant; there was no significant difference in other characteristics such as age, hyperthyroidism course, N stage, or capsule invasion (P>0.05) (*Table 2*).

Multivariate analysis

Multivariate binary logistic regression analysis was performed for variables that were statistically significant in the univariate analyses. The results showed that psTg [odds ratio (OR): 1.325, 95% confidence interval (CI): 1.135–1.547, P<0.001], maximum tumor diameter (OR: 2.428, 95% CI: 1.392–4.235, P=0.002), and pathology-confirmed combined HT (OR: 8.669, 95% CI: 1.877–40.038, P=0.006) were closely related to treatment response and were independent factors for ER. The logistic regression equation was as follows: Logit (P)=–4.620 + 0.282 × psTg + 0.887 × maximum diameter + 2.160 × pathology-confirmed combined HT. This equation was statistically significant (P<0.001, χ^2=55.49). For the above equation, a result less than 0.5 indicated possible ER, and a result greater than 0.5 indicated possible non-ER. The sensitivity, specificity, positive predictive value and negative predictive value were 82.1% (46/56), 69.7% (23/33), 82.1% (46/56) and 69.7% (23/33), respectively.

Power of the test for predicting ER by pathology-confirmed combined HT

The sensitivity of pathology-confirmed combined HT in predicting ER was 66.1% (37/56), the specificity was 78.8% (26/33), the positive predictive value was 84.1% (37/44), and the negative predictive value was 57.8% (26/45).

Discussion

Primary hyperthyroidism and DTC are the most common diseases of the endocrine system, and research on the relationship between the 2 has attracted increasing clinical attention. The incidence of DTC is increasing year by year worldwide, and it has become the seventh most common malignant tumor in China. The incidence of DTC in women is approximately 3 times that in men, and the peak age of onset is 50–54 years (1). In this study, the ratio of female patients to male patients was 3:1, and the mean age of the patients was 43.47±11.88, findings that were consistent with the above report.

It is currently believed that hyperthyroidism is an autoimmune disease caused by thyroid stimulating immunoglobulin (TSI). TSI has a similar structure to TSH and can bind to TSH receptor (TSHR) to produce a TSH-like effect that is stronger and more lasting than that produced by TSH, increasing the proliferation function of thyroid cells, increasing the expression of sodium-iodine symporter (NIS), producing excessive thyroid hormones; TSI is not inhibited by the pituitary gland, thereby stimulating the carcinogenesis of the thyroid gland. TSI can also stimulate angiogenesis, promote tumor development, and make tumors more aggressive (6). Previous studies have shown that the risk of DTC in patients with hyperthyroidism is 6.8 times higher than that in patients with normal thyroid function and that the longer the duration of hyperthyroidism is, the greater the risk of DTC and the worse the clinicopathological characteristics

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Table 1 Demographic characteristics of DTC patients with hyperthyroidism

Characteristic	Proportion n (%)
Male/female, n (%)	17 (19.1)/72 (80.9)
Age (years; $\bar{x}$±s)	43.47±11.88
Preoperative TSH [mU/L; M (P_{25}, P_{75})]	0.502 (0.130, 0.700)
Maximum tumor diameter [cm; M (P_{25}, P_{75})]	1.20 (0.75, 1.80)
Pathology-confirmed combined HT, n (%)	
Yes	44 (49.4)
No	45 (50.6)
Capsule invasion, n (%)	
Yes	52 (58.4)
No	37 (41.6)
T stage, n (%)	
T1	41 (46.1)
T2	10 (11.2)
T3	13 (14.6)
T4	25 (28.1)
N stage, n (%)	
N0	13 (14.6)
N1a	46 (51.7)
N1b	30 (33.7)
Risk stratification of recurrence, n (%)	
Medium risk	62 (69.7)
High risk	27 (30.3)
Lymph node metastasis rate [%; M (P_{25}, P_{75})]	37.00 (11.45, 50.00)
psTg [μg/L; M (P_{25}, P_{75})]	1.73 (0.51, 7.25)
First ^{131}I treatment dose [GBq; M (P_{25}, P_{75})]	3.70 (3.70, 4.44)
Efficacy evaluation, n (%)	
ER	56 (62.9)
BIR	10 (11.2)
SIR	14 (15.7)
IDR	9 (10.1)
Total number of cases, n (%)	89 (100.0)

In the test values column, normally distributed measurement data are expressed as the mean ± standard deviation, such as age at diagnosis. Skewed measurement data are expressed as the median [interquartile range], such as Preoperative TSH, Maximum tumor diameter, Lymph node metastasis rate, psTg, First ^{131}I treatment dose. Categorical data are expressed as frequency (percentage of all cases) [n (%)], including sex, Pathology-confirmed combined HT, Capsule invasion, T stage, N stage, Risk stratification of recurrence, Efficacy evaluation. DTC, differentiated thyroid cancer; TSH, serum thyroid stimulating hormone; HT, Hashimoto's thyroiditis; T, tumor; N, node; M, metastasis; psTg, preablative stimulated thyroglobulin before ^{131}I treatment, the lymph node metastasis rate refers to the proportion of metastases in all dissected lymph nodes; ER, excellent response; BIR, biochemical incomplete response; SIR, structural incomplete response; IDR, indeterminate response.

and prognosis (7-10). In this study, the course of hyperthyroidism did not affect the efficacy of ^{131}I (P=0.441, U=834.00), but patients who received preoperative drug treatment for hyperthyroidism were more likely to achieve ER (P=0.005, χ^2=10.62).

Serum Tg can be secreted by normal thyroid follicular epithelial cells or well-differentiated DTC cells and is affected by postoperative residual thyroid tissue, serum TSH, and TgAb levels. Previous studies have shown that changes in serum psTg levels are an important factor in disease remission, persistence, recurrence, and prognosis after DTC treatment and are an important indicator in efficacy evaluations, disease monitoring, and determining prognoses in long-term follow-up (11-13). In this study, multivariate analysis indicated that psTg was an independent factor for predicting ER (OR: 1.325; 95% CI: 1.135–1.547; P<0.001), which was consistent with previous research by Webb *et al.* in a meta-analysis of more than 4,000 cases of DTC (14).

HT is a chronic inflammatory response, and Ferrari *et al.* (15) proposed that in the process of the chronic inflammatory response, the infiltration of inflammatory cells and factors promotes the occurrence of DTC. Paparodis *et al.* (16) found that DTC is more common in patients with HT; however the related mechanism between HT and DTC has not yet been elucidated. Some studies have

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Table 2 Comparison of the clinicopathological characteristics of patients with primary hyperthyroidism combined with DTC in the ER group and non-ER group

Characteristics	ER group	Non-ER group	Test value	P value
Male/female (example)	6/50	11/22	6.875	0.009
Age (years; $\bar{x}$±s)	44.18±11.71	42.27±12.25	0.729[b]	0.468
Course of hyperthyroidism [month; M (P25, P75)]	10.5 (3.0, 33.0)	12.0 (3.0, 18.0)	834.000[a]	0.441
Preoperative TSH [mU/L; M (P25, P75)]	0.530 (0.135, 0.892)	0.264 (0.114, 0.516)	631.000[a]	0.013
Tumor maximum diameter [cm; M (P25, P75)]	1.0 (0.6, 1.5)	1.5 (1.0, 2.5)	1,234.500[a]	0.008
Pathology-confirmed combined HT (n)			16.716	<0.001
Yes	37	7		
No	19	26		
Capsule invasion (n)			0.586	0.444
Yes	31	21		
No	25	12		
T stage (n)			14.836	0.001
T1	42	12		
T2	2	6		
T3	4	8		
T4	8	7		
N stage (n)			0.329	0.872
N0	8	5		
N1a	28	18		
N1b	20	10		
Risk stratification of recurrence (n)			5.672	0.017
Medium risk	44	18		
High risk	12	15		
psTg [g/L; M (P25, P75)]	0.98 (0.14, 2.08)	9.28 (2.45, 14.39)	1,585.500[a]	<0.001
First ^{131}I treatment dose [GBq; M (P25, P75)]	3.70 (3.70, 4.44)	4.44 (3.70, 5.55)	11,140.000[a]	0.031
Hyperthyroidism treatment methods (n)			10.616	0.005
Imidazoles	42	19		
Propylthiouracil	6	0		
Untreated	8	14		
Total number of cases	56	33		

In the test values column, [a] is the U value, [b] is the *t* value, and the others are chi-square values. DTC, differentiated thyroid cancer; ER, excellent response; TSH, serum thyroid stimulating hormone; HT, Hashimoto's thyroiditis; T, tumor; N, node; M, metastasis; psTg, preablative stimulated thyroglobulin before ^{131}I treatment, the lymph node metastasis rate refers to the proportion of metastases in all dissected lymph nodes.

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found that DTC patients with HT have better pathological characteristics and prognoses, with a lower extraglandular invasion rate, lower central lymph node metastasis rate, and earlier tumor, node, metastasis (TNM) staging (17-19). Although HT is a factor that induces DTC, it is a protective factor for the prognosis of patients with DTC. Patients with HT are usually positive for TPOAb and TgAb, but some patients with a pathological diagnosis of HT are also negative for TgAb. The patients included in this study were all negative for TgAb, whether combined or not with HT diagnosed by postoperative pathology. The results show that the number of patients with pathology-confirmed combined HT in the ER group was higher than that in the non-ER group ($P<0.001$, $\chi^2=16.716$). Multivariate analysis showed that pathology-confirmed combined HT was an independent influencing factor for treatment efficacy, a finding that is consistent with previous research conclusions, suggesting that although patients with hyperthyroidism combined with DTC had a higher incidence rate in the presence of combined HT, their prognosis was good.

Thyroid tumor size is related to prognosis. Previous study (20) has reported that tumor diameter has a substantial impact on the prognosis of patients with DTC. In this study, tumor diameter was found to be an independent factor for predicting ER, suggesting that clinical attention should be paid to tumor size in patients with hyperthyroidism complicated with DTC.

This study has limitations. It is a single-center, small sample size, retrospective study. In addition, thyrotropin receptor antibody (TRAb) is an antibody specific to patients with hyperthyroidism. Most of the patients in this study had a short history of hyperthyroidism and did not receive systematic treatment for hyperthyroidism, only treatment to control thyroid function before surgery, and surgery was conducted when there were symptoms of hyperthyroidism, leading to incomplete results in the follow-up data; therefore, patients without symptoms were not included in the study. Therefore, expanding the sample size, extending the follow-up time, elucidating the molecular mechanisms and conducting prospective research will be the aims of future research.

Conclusions

In summary, this study demonstrate that most hyperthyroidism combined with DTC patients could get favorable clinical outcomes from ^{131}I treatment. The tumor diameter, pathology with Hashimoto's thyroiditis and psTg can predict patients with ER. These results are helpful to identify relatively high-risk patients with hyperthyroidism combined with DTC in clinical practice to a certain extent in early stage, so as to develop individualized treatment plans and optimize the follow-up protocols. In the future, further prospective and larger sample size studies are needed to provide more reliable evidence to support this idea.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-749/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-749/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-749/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (revised 2013). This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (No. QYFY WZLL 27241). Informed consent was not required as this was a retrospective study.

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