

# Age moderates the associations between TRAbs, free T3 and outcomes of Graves' disease patients with radioactive iodine treatment

Lusi Lu<sup>1</sup>  | Chenlu Gao<sup>2</sup> | Nan Zhang<sup>1</sup>

<sup>1</sup>Department of Endocrinology, School of Medicine, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China

<sup>2</sup>Department of Psychology and Neuroscience, Baylor University, Waco, TX, USA

## Correspondence

Nan Zhang, Department of Endocrinology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China.  
Email: 3198047@zju.edu.cn

## Abstract

**Objective:** This study aimed to explore whether age moderates the associations between TSH receptor antibodies (TRAbs) with thyroid hormones and remission in patients with Graves' disease (GD) who undergo radioactive iodine (RAI) treatment.

**Design:** A single-centre retrospective study.

**Patients:** A total of 435 eligible consecutive patients diagnosed with GD and treated with RAI therapy were included.

**Methods:** TRAbs and thyroid hormones prior to RAI were recorded. Pearson's correlation, t tests and analysis of covariance were conducted to identify the associations between TRAbs, thyroid hormones and remission. Moderation analyses were conducted to test age as a moderator.

**Results:** Overall, 75.4% of the patients achieved remission with a single dose of iodine-131. TRAb levels before RAI were positively correlated with the circulating thyroid hormones ( $p < 0.001$ ). Age moderated the association between TRAbs and free T3 (FT3) ( $P = .01$ ), but did not moderate the association between TRAbs and free T4 (FT4) ( $P = .07$ ). TRAb levels before RAI only significantly predicted remission status in young patients ( $P = .03$ ), but not in middle-aged ( $P = .36$ ) or older patients ( $P = .74$ ), after adjusting for covariates. When age was included as a continuous variable, moderation analyses revealed that the association between TRAbs and remission status was stronger in younger patients ( $P = .03$ ).

**Conclusions:** The majority of Graves' disease patients experienced a long-term remission following a single dose of iodine-131. Associations between TRAbs, FT3 and remission are moderated by age. TRAb level prior to RAI is a significant remission in younger patients, but not in middle-aged or older patients.

## KEYWORDS

age, Graves' disease, radioiodine, thyroid hormones, TRAbs

## 1 | INTRODUCTION

Graves' disease (GD) is a common thyroid condition that affects 0.5%-1.0% of the population in iodine-sufficient countries.<sup>1</sup> GD can occur at any age, although its incidence peaks between 30 and 60 years old.<sup>2</sup>

GD is characterized by the presence of TSH receptor antibodies (TRAbs) that stimulate thyroid cells, resulting in an overproduction of thyroid hormones.<sup>3</sup> TRAbs are pathognomonic for GD, which are detectable in almost every patient diagnosed with GD.<sup>4</sup> Furthermore, circulating TRAb levels correlate with the severity of GD and are useful predictors of prognosis.<sup>5</sup>

There are three treatment regimens available for GD, namely antithyroid drugs (ATDs), radioactive iodine (RAI) and thyroidectomy. RAI therapy has established safety and efficacy for treating GD. In practice, RAI therapy is often the preferred treatment in North America.<sup>6</sup> By contrast, it is generally used as the second-line therapy for patients experiencing relapses, persistent disease or complications of medical therapy in China.<sup>1</sup> Among the patients receiving a single dose of iodine-131, approximately 5%-15% require additional treatment,<sup>7,8</sup> although RAI is a safe and efficacious therapy to manage Graves' thyrotoxicosis. Many risk factors for failures of RAI have been identified, including male sex,<sup>9</sup> cigarette smoking,<sup>10</sup> large goitre size,<sup>11</sup> more severe thyrotoxicosis,<sup>12</sup> higher TRAb levels,<sup>13</sup> higher

thyroid peroxidase antibody (TPOAb) levels<sup>14</sup> and thyroid uptake on radionuclide scans.<sup>15</sup>

Our objective is to assess the associations between TRAbs before RAI with thyroid hormones and remission, and to explore whether age moderates the associations between TRAbs with thyroid hormones and remission in patients with Graves' disease who undergo RAI treatment.

## 2 | METHODS

### 2.1 | Study design and patients

In this retrospective cohort study, we used a data set of 645 patients who were diagnosed with GD and received RAI therapy between January 2017 and December 2018 at the Department of Endocrinology, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University, China. The Institutional Ethics Committee of the Sir Run Run Shaw Hospital approved this study. Diagnoses of GD were confirmed by a suppressed serum thyroid-stimulating hormone (TSH), along with elevated thyroid hormone levels in combination with elevated TRAb levels or a radionuclide scan compatible with Graves' disease. All GD patients who received their first RAI therapy in our department were included in the analyses. All patients had TRAbs, thyroid function, and

Variable	All patients (N = 645)	Follow-up data available (n = 435)	Follow-up data not available (n = 210)	P-value
Age, y	42.09 (14.02)	41.67 (13.77)	42.95 (14.51)	.28
Female gender, n (%)	493 (76.43%)	329 (75.63%)	164 (78.10%)	.49
Smoking				
Current	79 (12.25%)	51 (11.72%)	28 (13.33%)	.84
Former	19 (2.95%)	13 (2.99%)	6 (2.86%)	
Never	547 (84.81%)	371 (85.29%)	176 (83.81%)	
Duration of disease, y	4.93 (6.93)	4.32 (6.08)	6.20 (8.31)	.001**
TRAbs, IU/L	14.85 (12.94)	14.70 (11.93)	15.16 (14.87)	.68
TPOAb, IU/mL	490.77 (407.12)	501.82 (410.94)	467.36 (398.90)	.32
TSH, mIU/L	0.0027 (0.0255)	0.0028 (0.0226)	0.0027 (0.0309)	.95
Free T4, pmol/L	35.86 (12.94)	35.92 (13.04)	35.71 (12.75)	.85
Free T3, pmol/L	23.35 (14.66)	23.91 (15.00)	22.17 (13.90)	.16
Technetium uptake, %	16.63 (10.53)	16.57 (10.68)	16.74 (10.23)	.85
24-h radioactive iodine uptake, %	65.82(16.90)	65.59(17.19)	66.29(16.30)	.62

**TABLE 1** Comparison between Patients with Follow-up Data and Patients without Follow-up Data

Note: Data are presented as number (percentage) or mean (standard deviation). P-values represent the independent-sample t test and chi-square test results comparing patients who had follow-up data with patients who did not have follow-up data.

\*P ≤ .05.

\*\*P ≤ .01.

TPOAb levels measured 2 days before RAI therapy. Patients were not given ATDs within six months after RAI therapy. Two hundred and ten patients were lost to follow-up. Overall, the baseline characteristics of participants with follow-up data available were similar to those without (Table 1).

Radioactive iodine therapy ( $^{131}\text{I}$ ) was administered orally in the Department of Nuclear Medicine of Sir Run Run Shaw Hospital. The isotope dose was calculated based on the following formula:

$$\frac{\text{Intended dose } \left( \frac{\mu\text{Ci}}{\text{g}} \right) \times \text{thyroid gland weight (g)} \times 100}{24 \text{ hour radioactive iodine uptake (\%)}}$$

The intended dose was between 70 and 120  $\mu\text{Ci/g}$  of the thyroid, determined by physicians' clinical experience and the environmental impact of residue radiation doses.<sup>16</sup> Antithyroid drugs were ceased 3 (methimazole) days to 14 (propylthiouracil) days prior to RAI therapy.<sup>17</sup> All female patients during childbearing age underwent a pregnancy test (serum hCG) prior to the RAI therapy and received negative results.

## 2.2 | Data collection and outcome evaluation

Clinical and biochemical information was extracted from medical records. All relevant variables are listed in Table 2. Smoking

status was classified as nonsmokers, ex-smokers or current smokers. Laboratory assays for thyroid function, TRAbs and TPOAb were completed using Roche Elecsys electrochemiluminescence immunoassay. The reference ranges were as follows: TSH (0.35-4.94 mIU/L), free T4 (FT4; 8.96-18.94 pmol/L), free T3 (FT3; 2.57-5.57 pmol/L), TPOAb (0-5.61 IU/mL) and TRAbs (0-1.22 IU/L). Thyroid ultrasound was performed immediately before RAI therapy to assess thyroid volume.<sup>18</sup> Remission was defined as having an initiation of levothyroxine, TSH concentration above the reference limit or euthyroidism within 1 year after a single dose of RAI therapy.

## 2.3 | Statistical analysis

We first examined the distribution of variables; if a variable is non-normally distributed (ie absolute skewness > 2 or absolute kurtosis > 7),<sup>19</sup> then we transformed the variable to improve normality. Second, we used Pearson's correlation to investigate whether TRAb level and age were associated with FT3 and FT4. We investigated whether the associations between TRAbs, FT3 and FT4 were moderated by age via examining the associations in three age groups (based on tertiles of age distribution) and via moderation analyses (using bootstrapping; 5000 samples).<sup>20</sup> Covariates included sex, smoking status, ATD duration and pretreatment TPOAb level, which were chosen based on relevant literature.

**TABLE 2** Baseline Characteristics of Patients with Follow-up Data

Variable	All patients (n = 435)	Remission (n = 328)	No remission (n = 107)	P-value
Age, y	41.67 (13.77)	42.68 (13.24)	38.57 (14.94)	.01**
Female gender, n (%)	329 (75.63%)	253 (77.13%)	76 (71.03)	.20
Smoking, n (%)				
Current smoker	51 (11.72%)	33 (10.06%)	18 (16.82%)	.14
Former smoker	13 (2.99%)	9 (2.74%)	4 (3.74%)	
Nonsmoker	371 (85.29%)	286 (87.20%)	85 (79.44%)	
Duration of medical treatment, m	29.49 (50.32)	21.50 (41.92)	53.99 (64.36)	<.001**
Duration of disease, y	4.32 (6.08)	3.76 (5.94)	6.03 (6.20)	.001**
TRAbs, IU/L	14.70 (11.93)	14.02 (11.36)	16.77 (13.37)	.04*
TPOAb, IU/mL	501.82 (410.94)	501.98 (410.90)	501.33 (413.05)	.99
TSH, mIU/L	0.0028 (0.0226)	0.0023 (0.0210)	0.0043 (0.0270)	.42
Free T4, pmol/L	35.92 (13.04)	34.77 (11.91)	39.41 (15.54)	.001**
Free T3, pmol/L	23.91 (15.00)	22.51 (14.29)	28.15 (16.29)	.001**
Technetium uptake, %	16.57 (10.68)	14.26 (7.87)	23.68 (14.43)	<.001**
Dose of $^{131}\text{I}$ , mci	9.65 (1.96)	9.46 (1.73)	10.21 (2.46)	.001**
24-h radioactive iodine uptake, %	65.59(17.19)	65.09 (17.38)	67.11 (16.58)	.29
Thyroid volume, ml	26.81 (21.10)	21.21 (10.59)	43.97 (32.91)	<.001**

Note: Data are presented as number (percentage) or mean (standard deviation). P-values represent the independent-sample t test and chi-square test results comparing patients who experienced remission with patients did not experience remission.

\* $P \leq .05$ .

\*\* $P \leq .01$ .

Next, we used independent-samples *t* tests and analysis of covariance (ANCOVA) to compare TRAb levels between patients with remission and patients without remission. Last, we used ANCOVA and bootstrapping moderation analyses to test whether the relationship between TRAbs and remission status was moderated by age, while controlling for covariates. Covariates included sex, smoking status, ATD duration, dose of  $^{131}\text{I}$ , pretreatment thyroid function and pretreatment TPOAb levels, which were chosen based on previous literature. Because dose of  $^{131}\text{I}$  was calculated based on thyroid weight, and it was significantly correlated with both thyroid weight ( $r = 0.39, P < .001$ ) and thyroid volume ( $r = 0.45, P < .001$ ), we did not include thyroid weight or volume as additional covariates.

All statistical analyses were performed using SPSS software (version 26); Figures 1 and 2 were constructed using GraphPad Prism 8. All statistical tests were two-tailed, and results with  $P \leq .05$  were considered significant.

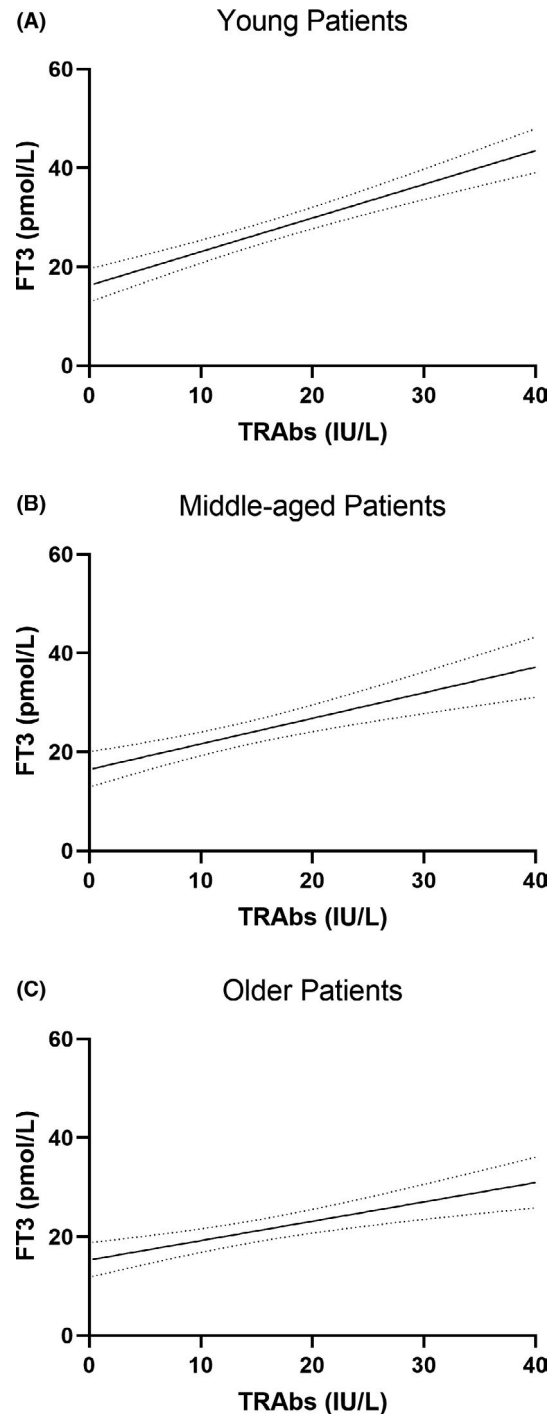
### 3 | RESULTS

#### 3.1 | Characteristics of the patients

A total of 435 consecutive eligible patients with follow-up data were included in analyses (Table 2;  $M_{\text{age}} = 41.67$  years,  $SD = 13.77$  years; 75.63% female; 11.72% current cigarette smokers). We categorized patients into three age groups based on tertiles of age distribution. Young patients were 17.2 to 33.66 years old ( $n = 145, M_{\text{age}} = 26.6$  years,  $SD_{\text{age}} = 4.4$  years); middle-aged patients were 33.67 to 48.36 years old ( $n = 145, M_{\text{age}} = 40.9$  years,  $SD_{\text{age}} = 4.3$  years); and older patients were 48.41 to 80.7 years old ( $n = 145, M_{\text{age}} = 57.5$  years,  $SD_{\text{age}} = 7.3$  years).

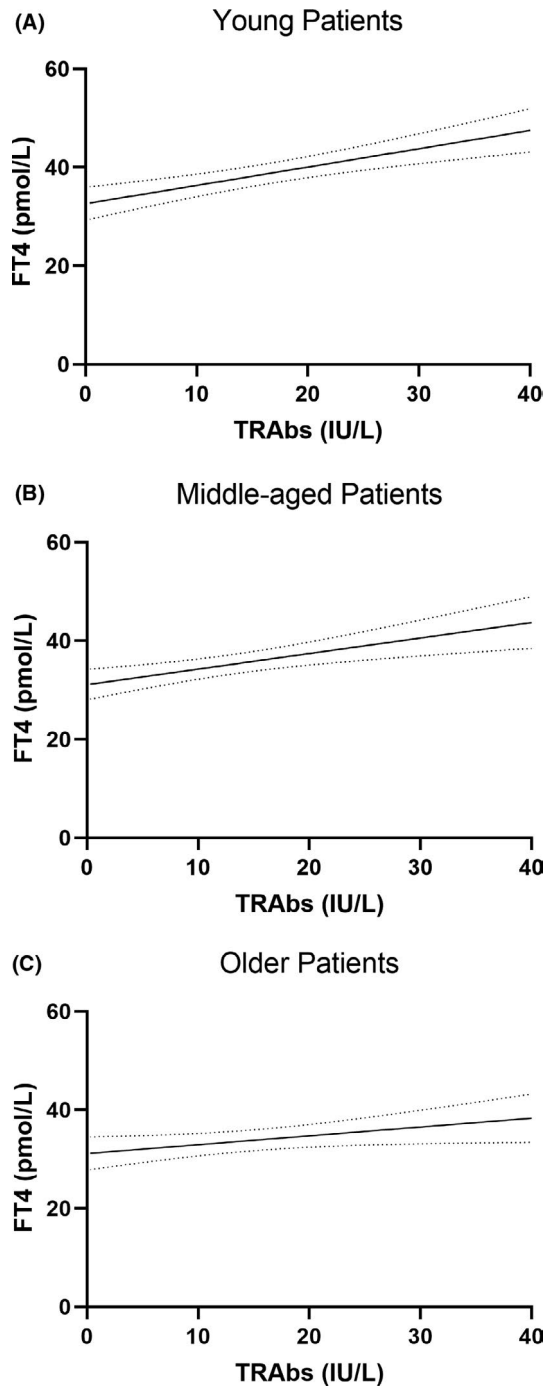
Among the eligible patients, 342 (78.62%) were treated with anti-thyroid drugs prior to RAI. Among the 342 patients, 300 (87.72%) patients were initially treated with methimazole; 28 of the 300 patients switched to propylthiouracil (PTU) therapy during the course of the treatment. In addition, 42 (12.28%) of the 342 patients were initially treated with PTU and 20 of them switched to methimazole. The reasons for RAI therapy are summarized in Table 3. We found that the complications of ATD treatment, including allergy, hepatic dysfunction and leukopenia, were the primary reasons for RAI therapy. The median duration of ATDs treatment was 12 months (interquartile range: 1-48,  $M = 36.66, SD = 53.71$  months) prior to receiving RAI therapy.

During a median follow-up time of 16 months (interquartile range: 9-23,  $M = 16.44, SD = 8.78$  months) after RAI therapy, 328 (75.4%) patients had their hyperthyroidism condition resolved. Of the 107 patients who had unresolved hyperthyroidism, 63 patients received a second dose of RAI therapy, 27 patients accepted antithyroid drug treatment, and 17 patients did not receive further treatment for persistent subclinical hyperthyroidism. Furthermore, 318 patients in the remission group transformed to hypothyroidism and 10 patients remained euthyroid. Among the 318 patients in the remission group, the median time from RAI administration to hypothyroidism was 3 months (interquartile range: 2-4,  $M = 4.15, SD = 3.19$  months). Among all



**FIGURE 1** The associations between TRAbs and FT3 in young (17.2-33.66 years old; A), middle-aged (33.67-48.36 years old; B), and older patients (48.41-80.7 years old; C). The black lines represent the regression lines and dotted lines represent 95% confidence intervals of the regression lines. TRAbs significantly predicted FT3 levels in all three age groups ( $ps < 0.001$ )

studied patients, 21 patients had pre-existing inactive Graves' ophthalmopathy (GO); 1 patient had pre-existing active GO and received prophylactic glucocorticoid treatment. Of the 22 patients, none experienced worsening of their GO after RAI. Additionally, none of the patients experienced new GO onset after RAI.



**FIGURE 2** The associations between TRAbs and FT4 in young (17.2–33.66 years old; A), middle-aged (33.67–48.36 years old; B), and older patients (48.41–80.7 years old; C). The black lines represent the regression lines and dotted lines represent 95% confidence intervals of the regression lines. TRAbs significantly predicted FT4 levels in young and middle-aged patients, but not in older patients

**3.2 | The correlation between TRAbs and FT3**

First, we observed that age did not correlate with TRAb levels [ $r(433) = -0.07, P = .17$ ], but negatively correlated with FT3,  $r(429) = -0.23, P < .001$ . Moving from this observation, the correlation between serum TRAb and FT3 levels before RAI was analysed. We found that

**TABLE 3** Reasons for Radioiodine Therapy

Reason for radioiodine therapy	Number of participants
ATD complications (allergy, hepatic dysfunction, leukopenia)	135
Poor response/unable to withdraw ATDs	87
Relapse	85
Ineligible for ATDs (hepatic dysfunction and leukopenia)	47
Patient preference	39
Poor compliance with ATDs	23
Cardiovascular comorbidities	18
Diabetes comorbidity	1

serum TRAb levels correlated with the circulating concentrations of FT3,  $r(429) = 0.43, P < .001$ . This association was independent of sex, smoking status, TPOAb levels and duration of ATD treatment,  $r_p(418) = 0.42, P < .001$ .

Further stratification by age tertiles showed that TRAbs and FT3 were positively correlated in all three age groups after controlling for sex, smoking status, TPOAb levels and duration of ATD treatment (young:  $r_p(138) = 0.56, P < .001$ ; middle-aged:  $r_p(135) = 0.36, P < .001$ ; older:  $r_p(133) = 0.34, P < .001$ ; Figure 1). However, TRAbs seemed to be more strongly associated with FT3 among young patients; in addition, bootstrapping moderation analyses showed that age, as a continuous variable, significantly moderated the association between TRAbs and FT3 ( $b = -0.01, SE = 0.004, P = .01$ ), after controlling for sex, smoking status, TPOAb levels and duration of ATD treatment.

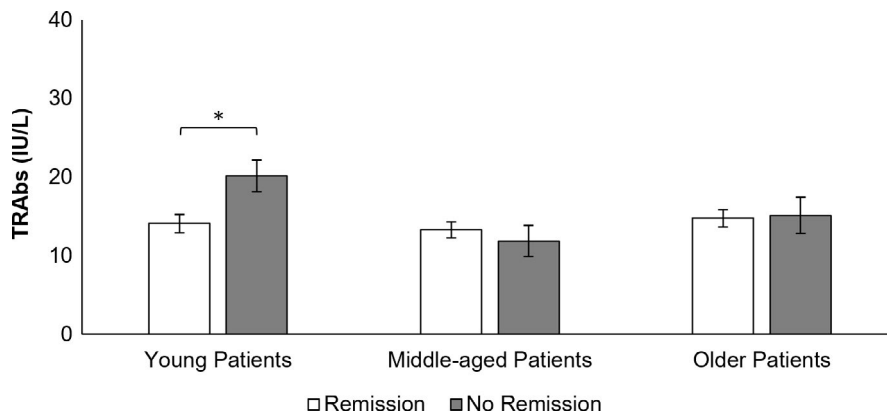
**3.3 | The correlation between TRAbs and FT4**

Next, age negatively predicted FT4 levels,  $r(429) = -0.20, P < .001$ . We then found that TRAb levels were correlated with FT4 levels,  $r(429) = 0.27, P < .001$ . The correlation remained significant after controlling for sex, smoking status, TPOAb levels and duration of ATD treatment,  $r_p(418) = 0.25, P < .001$ .

Age stratification showed that TRAbs significantly correlated with FT4 levels in young and middle-aged patients, but not in older patients, after adjusting for sex, smoking status, TPOAb levels and duration of ATD treatment (young:  $r_p(138) = 0.33, P < .001$ ; middle-aged:  $r_p(135) = 0.25, P = .004$ ; older:  $r_p(133) = 0.14, P = .10$ ; Figure 2). However, bootstrapping moderation analyses showed that age, as a continuous variable, did not significantly moderate the association between TRAbs and FT4 ( $b = -0.01, SE = 0.003, P = .07$ ).

**3.4 | Relationship between TRAbs and the efficacy of radioiodine therapy**

A significant difference in the TRAbs before RAI was observed in the group that achieved remission compared with the group that did not achieve remission,  $t(433) = 2.08, P = .04, d = 0.23$ . Through analyses



**FIGURE 3** TRAbs levels differed between remission and no remission groups in young patients (17.2–33.66 years old), but not in middle-aged (33.67–48.36 years old) or older patients (48.41–80.7 years old). Error bars: standard error. \* $P \leq .05$

of TRAbs and the efficacy of RAI therapy, we found differences across age groups. Further stratification by age tertiles showed differences among age groups such that TRAb levels only significantly predicted remission status in young patients ( $F(1, 136) = 4.86, P = .03$ , partial  $\eta^2 = 0.03$ ) and did not predict remission in middle-aged patients ( $F(1, 133) = 0.27, P = 0.61$ , partial  $\eta^2 = 0.002$ ) or older patients ( $F(1, 131) = 0.16, P = 0.69$ , partial  $\eta^2 = 0.001$ ), after adjusting for TSH, TPOAb, ATD duration, dose of  $^{131}\text{I}$ , smoking status and sex (Figure 3). Bootstrapping moderation analyses showed that age, as a continuous variable, significantly moderated the association between TRAbs and remission status, after adjusting for the same covariates ( $b = -0.002, SE = 0.001, P = .03$ ). These results suggested that the association between TRAbs and remission status was stronger in younger patients.

## 4 | DISCUSSION

In the present retrospective cohort study of Graves' disease patients treated with RAI, we found that 75.4% of the patients achieved remission with a single dose of iodine-131. Simultaneously, TRAb levels before RAI were associated with circulating pretreatment FT3 levels, FT4 levels and remission. The association between TRAb levels and FT3 levels gradually weakens with age. Additionally, increasing TRAb levels were associated with nonremission in young patients, but not in middle-aged and older patients.

The remission rate after the administration of RAI in our study is comparable to that in previous studies.<sup>8,16</sup> Our findings suggest that the increasing TRAb levels were associated with higher FT3 and FT4 levels<sup>21</sup> and lower likelihood of remissions,<sup>13,22</sup> consistent with previous studies on GD outcomes. However, only a few studies to date specifically examined age as a potential moderator. Ageing is involved in the pathophysiology of GD, such that the onset of GD at younger ages would yield higher free thyroxine levels<sup>23,24</sup> and worse prognostic.<sup>12</sup>

TRAbs are autoantibodies that combine with the TSHR to exert stimulatory, inhibitory or neutral effects. In our study, lower TRAb titre was associated with a greater likelihood of remission in young patients, but not in middle-aged or older patients. One possible explanation is that older patients are more likely to experience altered TRAb biological activity. As we have seen, ageing can modify the set point of the hypothalamus-pituitary-thyroid axis.<sup>25,26</sup> In our study, TRAbs

were positively associated with FT3 levels, and this association gradually weakened as age increased. TRAbs were also positively associated with FT4 levels, but the association was not moderated by age.

Even in people without thyroid diseases, older age has been associated with increases in serum TSH concentrations, with no change in FT4 concentrations.<sup>27</sup> Thus, we cannot exclude the possibility that in older patients, the responsiveness of the thyroid gland to TSH becomes diminished.<sup>28</sup> Similar to TSH, TRAbs also combine with TSHR in the thyroid gland to exert biological effects. Therefore, the responsiveness of TSHR and the thyroid gland to TRAb stimulation may decline with age. However, further studies are required to elucidate the exact mechanisms.

Our findings suggest that circulating TRAb levels may not be a good predictor of patients' outcomes after a single dose of RAI in middle-aged and older patients with GD. Therefore, the interpretation of thyroid parameters is potentially complicated in middle-aged and older patients. As TRAbs can ideally predict the remission rate in younger patients, RAI may be a good therapeutic choice for young patients with low TRAbs.

There were several limitations that should be considered. Due to China's national policies of graded diagnoses and treatments, patients living in rural areas will return to their local hospitals for follow-up assessments after RAI therapy. This contributes to the attrition in this retrospective study (around 33%; Table 1); although the characteristics of patients with follow-up data available were similar to those without follow-up date, the findings of the present study may still be less generalizable to the general patient populations. Another limitation is that the categorization of age based on tertiles does not match clinical definitions of age groups. In addition, the assay we used cannot be used to distinguish stimulatory, inhibitory and neutral TRAbs. Finally, given the observational characteristic of our study, we cannot rule out the possibility of residual confounding.

In summary, our study suggests that the majority of GD patients experienced long-term remission following a single dose of RAI. Furthermore, we investigated the differences in the predictive power of TRAbs among younger, middle-aged and older GD patients. In younger patients, TRAbs before RAI are a significant predictor of remission. These findings can serve as useful guidance in clinical practice in treating GD. Future studies are needed to replicate our findings in different populations. Also, it will be necessary

in the future to investigate the exact mechanisms that underlie our findings.

### CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### ORCID

Lusi Lu  <https://orcid.org/0000-0001-7631-1102>

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