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Original Article

Effect of different doses of intravenous glucocorticoid therapy on metabolic safety in patients with thyroid-associated ophthalmopathy

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Abstract: Objective: To evaluate the efficacy of different-doses of intravenous glucocorticoid therapy in thyroid-associated ophthalmopathy (TAO) and its impact on metabolic safety. Methods: A total of 240 patients with active TAO were retrospectively analyzed and grouped by cumulative glucocorticoid dose: high-dose (n=112) and low-dose (n=128). Systematic evaluations were performed at baseline and 4 weeks after treatment. Ophthalmologic assessments included visual acuity, exophthalmos (Hertel exophthalmometer), Clinical Activity Score (CAS), diplopia severity (Gorman score), extraocular muscle motility, and magnetic resonance imaging (MRI) for muscle thickness and signal intensity. Hematologic tests included thyroid function (FT3, FT4, TSH), thyrotropin receptor antibody (TRAb), fasting blood glucose, HbA1c, and lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C). Statistical analyses employed Kolmogorov-Smirnov tests, t-tests or Mann-Whitney U tests, chi-square tests, and logistic regression with inverse probability weighting (IPWT) to assess risk factors. Results: Both groups showed significant CAS reduction after 4 weeks (P<0.001), with greater decreases in the high-dose group (mean difference >1.5 points, P<0.05). Diplopia remission was higher in the high-dose group versus low-dose (36.6% vs 24.2%, P<0.05). Exophthalmos reduction averaged 2.3±0.9 mm (high-dose) versus 1.6±0.7 mm (low-dose) (P<0.01). MRI revealed greater reductions in muscle thickness and signal intensity in the high-dose group (P<0.05). Metabolically, the high-dose patients exhibited more frequent elevations in fasting glucose, HbA1c, and lipid abnormalities (P<0.05). Logistic regression confirmed high-dose therapy as an independent risk factor for metabolic abnormalities (OR=2.15, 95% CI: 1.32-3.49, P<0.01). Conclusions: Different-doses of intravenous glucocorticoids improved TAO inflammatory activity and visual function. Within 4 weeks, high-dose regimens achieved stronger early improvements - particularly in patients with higher baseline inflammation or SIR/TRAb levels - but increased glucose and lipid abnormalities.

Keywords: Thyroid-associated ophthalmopathy, glucocorticoids, metabolic safety, clinical activity score, diplopia, magnetic resonance imaging

Introduction

Thyroid-associated ophthalmopathy (TAO) is an autoimmune disorder closely linked to thyroid dysfunction, commonly occurring in patients with hyperthyroidism, hypothyroidism, or fluctuating thyroid function [1]. Clinical manifestations include eyelid edema, exophthalmos, diplopia, and in severe cases, optic nerve compression leading to irreversible visual impairment [2]. The pathogenesis involves complex mechanisms including immune-inflammatory responses and orbital fat and extraocular muscle proliferation. Disease progression is often accompanied by declining quality of life and increased psychological burden [3]. Therefore, effective inflammatory activity control, symptom alleviation, and disease progression delay remain primary focuses of clinical practice and research.

Among therapeutic approaches, glucocorticoids (GCs) are established as first-line treatment for moderate to severe active TAO due to their potent immunosuppressive and anti-inflammatory effects [4]. Intravenous adminis-

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tration achieves higher plasma concentrations within shorter timeframes compared to oral routes, reduces local inflammatory responses, and is associated with fewer overall adverse events [5]. However, optimal dosing regimens remain controversial. Some studies advocate high-dose protocols for superior ocular activity improvements, yet this approach increases risks of metabolic disturbances and systemic adverse reactions. Alternatively, moderate-dose or fractionated regimens may provide better safety profiles but may compromise therapeutic efficacy [6].

Glucocorticoid metabolic side effects are well-documented across various diseases, including glucose fluctuations, exacerbated insulin resistance, and dyslipidemia [7]. For TAO patients, these risks require particular attention as this population frequently presents with underlying metabolic abnormalities or compromised endocrine function. Clinically, physicians must balance efficacy-focused versus safety-focused approaches. Current research predominantly emphasizes efficacy evaluation, with insufficient systematic comparisons of different intravenous glucocorticoid doses regarding metabolic effects [8, 9]. Evidence-based data for Chinese populations remain particularly scarce.

Treatment extends beyond inflammation elimination or exophthalmos control. Long-term health and quality of life are equally important for patients. If high-dose applications achieve short-term efficacy but cause irreversible metabolic damage, their clinical value becomes questionable. Achieving acceptable ocular improvements with moderate-dose treatment while reducing metabolic burden may represent a more individualized medical approach [10]. Therefore, dosage optimization encompasses not only pharmacologic and clinical efficacy considerations but also comprehensive patient health management.

This study aimed to compare the differential effect of various intravenous glucocorticoid doses on glucose and lipid metabolic values, combined with clinical efficacy assessment, to provide evidence-based support for dose selection. This approach enables physicians to make informed decisions balancing efficacy and safety when developing treatment plans. Essentially, this study addresses the question: "Which treatment approach truly benefits patients long-term?"

Materials and methods

Sample size calculation

We used the multicenter, randomized, double-blind trial by Bartalena et al. [11] as a starting point. That study evaluated the efficacy of different cumulative doses of intravenous methylprednisolone monotherapy for moderate-to-severe and active thyroid-associated ophthalmopathy. Based on the 52% response rate in the high-dose group (7.47 g) and the 15% natural improvement rate reported in placebo-controlled groups in the literature, we set the expected response rate in the experimental group (Pt) at 0.52, and for the control group (Pc) at 0.15. Using a two-sided test with a significance level $\alpha=0.05$ ($Z\alpha=1.96$), power $1-\beta=0.90$ ($\beta=0.10$, $Z\beta=1.28$), and group allocation ratio $k=1$, the calculated sample size was 32 patients per group. Accounting for approximately 15% dropout and refusal rates, we determined that 38 patients were required in each experimental and control group, totaling 76 enrolled patients.

Patient source

We retrospectively analyzed 240 patients with moderate to severe active TAO who visited our institution from July 2021 to May 2024, dividing them into high-dose group (n=112) and low-dose group (n=128) according to cumulative glucocorticoid dosage. This study was approved by Xi'an People's Hospital (Xi'an Fourth Hospital) medical ethics committee.

Inclusion and exclusion criteria

Inclusion criteria: (1) Age ≥18 years; (2) Diagnosed with thyroid-associated ophthalmopathy in active moderate-to-severe phase [12]; (3) Planned to receive intravenous glucocorticoid first-line treatment; (4) Relatively stable thyroid function; (5) Complete baseline metabolic assessment available.

Exclusion criteria: (1) Recent use of systemic immunosuppressants or systemic glucocorticoid therapy; (2) Presence of uncontrolled metabolic or medical diseases (diabetes, hypertension, severe dyslipidemia, etc.); (3) Severe hepatic or renal dysfunction or active infection; (4) Pregnancy, lactation, or glucocorticoid allergy; (5) Body weight changes exceeding 10% during treatment; (6) Patients who received any

concomitant medications or therapies during the study period that could influence TAO outcomes or metabolic indices (e.g., systemic immunomodulators, hypoglycemic agents, lipid-lowering drugs, or other glucocorticoid regimens) were excluded.

Treatment protocol

This study enrolled 240 patients with thyroid-associated ophthalmopathy, divided into high-dose and low-dose groups based on intravenous glucocorticoid dosage. High-dose group: Patients received intravenous methylprednisolone pulse therapy at 1.0 g weekly for 6 weeks, followed by dose reduction to 0.5 g weekly for 6 weeks. Total treatment duration was 12 weeks with a cumulative dose of 9.0 g. Low-dose group: Patients received conventional-dose intravenous methylprednisolone therapy at 0.5 g weekly for 6 weeks, followed by dose reduction to 0.25 g weekly for 6 weeks. Total treatment duration was 12 weeks with a cumulative dose of 4.5 g. Anti-thyroid medication dosages were appropriately adjusted throughout treatment according to patients' thyroid function status.

Clinical data collection

Patient clinical data were obtained from hospital electronic medical records and outpatient follow-up examination records. Data collection encompassed several domains: (1) General demographic information: patient age, gender, body mass index (BMI), smoking history, and other baseline characteristics; (2) Ocular disease parameters: Clinical Activity Score (CAS), exophthalmos measurements, extraocular muscle involvement, visual acuity, and imaging studies including MRI extraocular muscle thickness and signal changes. Diplopia was assessed using Gorman subjective diplopia scoring to ensure evaluation consistency; (3) Metabolic and comorbidity status: blood pressure, glucose levels, lipid profiles, and other metabolic indicators, along with documentation of diabetes, hypertension, dyslipidemia, and other underlying conditions; (4) Adverse event documentation: metabolic complications during treatment including weight changes, glucose fluctuations, blood pressure elevation, and lipid abnormalities, plus other treatment-related events.

Two researchers independently collected all data with cross-verification procedures. Disagreements were resolved by a third researcher to ensure data accuracy and completeness.

Functional scoring

Functional assessment of thyroid-associated ophthalmopathy used CAS [13] and Gorman subjective diplopia scoring [14]. CAS evaluates inflammatory activity through 7 indicators: eyelid erythema and swelling, conjunctival hyperemia, edema, and spontaneous retrobulbar pain. Each item scores 1 point, with total scores ranging from 0-7 points. Higher scores indicate greater inflammatory activity and active disease phases. Gorman subjective diplopia scoring assesses diplopia severity on a 0-3 point scale: 0 point indicating no diplopia, 1 point for intermittent diplopia, 2 points for constant diplopia, and 3 points for severe diplopia. Higher scores represent more severe symptoms with greater impact on daily functioning.

Examination items

All patients underwent comprehensive evaluations before treatment initiation (treatment-naïve baseline) and 4 weeks post-treatment. Ophthalmological assessments included visual acuity testing, exophthalmos measurement using Hertel exophthalmometer, CAS evaluation, extraocular muscle movement assessment, and diplopia determination according to Gorman subjective diplopia scoring. Imaging studies utilized MRI with a Philips Achieva 3.0T scanner to measure extraocular muscle thickness and signal changes.

Laboratory investigations included thyroid function tests (FT3, FT4, TSH), thyroid-related antibodies (TRAb), and metabolic parameters including fasting blood glucose, HbA1c, and lipid profiles comprising total cholesterol (TC), triglycerides (TG), HDL-C, and LDL-C. All hematologic analyses were performed using automated biochemical analyzer (Hitachi 7600) and automated immunochemiluminescence analyzer (Abbott Architect i2000). These comprehensive assessments evaluated patients' thyroid function status, ocular involvement severity, and metabolic safety profiles.

Inverse probability weighting (IPWT)

To reduce treatment-selection bias, we estimated propensity scores (PS) for receiving the high-dose regimen using multivariable logistic regression and constructed stabilized inverse

probability weights (IPTW). For patients in the high-dose group, the weight was calculated as $\omega_i = \frac{P(T=1)}{\hat{e}(X_i)}$, and for those in the low-dose group as $\omega_i = \frac{P(T=0)}{1-\hat{e}(X_i)}$, where $\hat{e}(X_i)$ is the estimated propensity score for individual *i*. The covariate set included potential confounders covering demographics (age, disease duration, sex, smoking history, drinking history, marital status), baseline metabolic/cardiometabolic status (BMI, systolic and diastolic blood pressure, FBG, 2hPG, TC, TG, LDL-C, HDL-C, diabetes history, and HbA1c when available), thyroid function and immunology (FT3, FT4, TSH, TRAb), and disease activity or imaging/ocular measures (CAS, mean SIR, exophthalmos of both eyes, and mean diameters of extraocular muscles on both sides). Variables marked with were dichotomized using thresholds determined by our ROC analysis (age = 48 years, disease duration = 10 years, TRAb = 10.18 IU/L, CAS = 4 points, SIR = 1.75), while other continuous variables were entered in their original scale. To limit extreme weight influence, we trimmed the weights at the 1st and 99th percentiles (range [0.814, 1.204]). Weighted logistic regression was then used to assess the treatment effect, and a survey/quasibinomial model with robust standard errors was applied as a sensitivity check. Covariate balance before and after weighting was evaluated using standardized mean differences (SMD), with SMD <0.1 considered acceptable. The main analysis used complete cases, and variables with <10% missingness were further examined through multiple-imputation sensitivity analysis, which produced consistent results.

Efficacy evaluation

Therapeutic efficacy was evaluated according to standardized clinical criteria. Cured was defined as complete resolution of ocular symptoms and signs, with a CAS decrease of ≥2 points and a reduction in exophthalmos of ≥2 mm. Markedly effective indicated clear improvement in ocular symptoms and signs, a noticeable reduction in exophthalmos, and a decrease in CAS score. Effective referred to partial improvement of ocular symptoms or signs, with little or no change in CAS score but some improvement in exophthalmos. Ineffective was defined as no improvement or worsening of ocular symptoms, signs, or exophthalmos, or an unchanged or increased CAS score. The overall response rate was calculated as the sum of cured, markedly effective, and effective cases. All evaluations were independently assessed and recorded by the same endocrinology specialist to ensure consistency [13].

Outcome measures

Study endpoints were categorized as primary and secondary outcomes. Primary endpoints included ocular disease activity assessed by CAS for inflammatory activity evaluation; diplopia severity measured by Gorman subjective diplopia score to determine symptom impact on daily functioning; exophthalmos measurements evaluating orbital tissue involvement; visual acuity changes reflecting disease effect on visual function; and extraocular muscle MRI assessment (thickness and signal intensity) analyzing inflammatory edema and fibrosis progression.

Secondary endpoints comprised thyroid function indicators (FT3, FT4, TSH, TRAb) assessing thyroid status and immune activity; metabolic indicators (fasting glucose, HbA1c, lipid profiles) monitoring glucocorticoid treatment effects on metabolic safety; blood pressure measurements observing cardiovascular risk changes; BMI reflecting treatment impact on weight and metabolism; and adverse event documentation evaluating treatment tolerability and safety profiles across different dosing regimens.

Statistical analysis

Statistical analyses were performed using R 4.3.2 software. Continuous variables underwent Kolmogorov-Smirnov (K-S) testing to determine distribution patterns. Normally distributed data were expressed as mean ± standard deviation ($\bar{x} \pm s$), with between-group comparisons using independent samples t-tests and within-group pre- and post-treatment comparisons using paired t-tests. Non-normally distributed data were presented as median (interquartile range), with between-group comparisons using Mann-Whitney U tests and within-group comparisons using Wilcoxon signed-rank tests. Categorical data were expressed as frequencies and percentages, with between-group comparisons using χ^2 tests or Fisher's exact tests.

Table 1. Comparison of baseline characteristics between high-dose and low-dose groups

Variable	Total	High-dose group (n=112)	Low-dose group (n=128)	Test statistic	*P* value
Age (years)	45.00 [35.00, 54.25]	44.00 [35.00, 55.00]	45.50 [35.75, 54.00]	0.153	0.878
BMI (kg/m^2)	24.20 [21.81, 26.36]	24.44 [21.57, 26.36]	23.98 [21.88, 26.32]	0.478	0.633
Disease duration (years)	9.00 [6.00, 12.00]	10.00 [6.00, 12.00]	9.00 [6.00, 12.00]	0.108	0.914
Systolic BP (mmHg)	127.37±8.54	128.15±10.03	126.69±6.95	-1.328	0.186
Diastolic BP (mmHg)	77.19±6.25	77.35±6.56	77.05±5.99	-0.372	0.71
T3 (nmol/L)	1.85 [1.35, 2.42]	1.97 [1.44, 2.47]	1.75 [1.13, 2.32]	1.746	0.081
T4 (nmol/L)	103.45 [75.61, 126.72]	106.13 [74.11, 130.96]	102.03 [78.46, 121.58]	0.622	0.534
FT3 (pmol/L)	5.67±2.31	5.63±2.48	5.70±2.15	0.214	0.831
FT4 (pmol/L)	17.40±6.62	17.91±7.55	16.95±5.69	-1.112	0.267
TSH (mIU/L)	1.29 [0.83, 1.80]	1.31 [0.80, 1.78]	1.26 [0.88, 1.82]	0.081	0.935
TRAb (IU/L)	9.79 [5.78, 12.84]	9.85 [5.90, 12.70]	9.64 [5.75, 12.89]	0.126	0.9
Gender				0.407	0.523
Male	119 (49.58%)	58 (51.79%)	61 (47.66%)		
Female	121 (50.42%)	54 (48.21%)	67 (52.34%)		
Smoking history				0.539	0.463
Yes	72 (30.00%)	31 (27.68%)	41 (32.03%)		
No	168 (70.00%)	81 (72.32%)	87 (67.97%)		
Alcohol consumption				0.335	0.563
Yes	40 (16.67%)	17 (15.18%)	23 (17.97%)		
No	200 (83.33%)	95 (84.82%)	105 (82.03%)		
Diabetes history				0.223	0.637
Yes	26 (10.83%)	11 (9.82%)	15 (11.72%)		
No	214 (89.17%)	101 (90.18%)	113 (88.28%)		
Marital status				0.58	0.446
Married	217 (90.42%)	103 (91.96%)	114 (89.06%)		
Other	23 (9.58%)	9 (8.04%)	14 (10.94%)		

Note: BMI, Body mass index; T3, triiodothyronine; T4, thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TRAb, thyrotropin receptor antibody.

To explore multifactorial effects on efficacy and safety outcomes, logistic regression analysis examined risk factors affecting patient diplopia, combined with inverse probability of treatment weighting (IPWT) to balance potential baseline differences between groups. All statistical tests were two-sided, with P<0.05 considered significant.

Results

Baseline characteristics comparison

High-dose and low-dose groups demonstrated comparable demographic, clinical, and biochemical indicators at baseline, with no statistically significant differences across all variables. Age (P=0.878), BMI (P=0.633), disease duration (P=0.914), systolic blood pressure (P=0.186), diastolic blood pressure (P=0.710), triiodothyronine (P=0.081), thyroxine (P=0.534), FT3 (P=0.831), FT4 (P=0.267), TSH (P=0.935), TRAb (P=0.900), gender (P=0.523), smoking history (P=0.463), alcohol consumption (P=0.563), diabetes history (P=0.637), and marital status (P=0.446) showed no significant differences (**Table 1**).

Pre-treatment ocular and metabolic indicators comparison

Both groups exhibited comparable pre-treatment ocular and metabolic indicators without significant differences. CAS (P=0.697), right eye exophthalmos (P=0.753), left eye exophthalmos (P=0.475), right extraocular muscle average diameter (P=0.800), left extraocular muscle average diameter (P=0.535), extraocu-

Table 2. Comparison of pre-treatment ocular and metabolic indicators between high-dose and low-dose groups

Variable	Total	High-dose group (n=112)	Low-dose group (n=128)	Test statistic	*P* value
Pre-treatment CAS score (points)	3.00 [3.00, 4.00]	3.00 [3.00, 4.00]	3.00 [3.00, 4.00]	0.596	0.551
Pre-treatment right exophthalmos (mm)	19.06±2.45	19.19±2.60	18.96±2.33	-0.716	0.475
Pre-treatment left exophthalmos (mm)	19.19±2.15	19.10±2.28	19.27±2.04	0.622	0.535
Pre-treatment right extraocular muscle average diameter (mm)	5.33±0.97	5.39±0.91	5.29±1.03	-0.804	0.422
Pre-treatment left extraocular muscle average diameter (mm)	5.10±0.89	5.01±0.80	5.17±0.96	1.418	0.157
Pre-treatment extraocular muscle average SIR	1.73±0.31	1.76±0.30	1.71±0.31	-1.385	0.167
Pre-treatment FBG (mmol/L)	4.59±0.63	4.57±0.62	4.60±0.64	0.468	0.641
Pre-treatment 2hPG (mmol/L)	6.24±1.33	6.27±1.40	6.21±1.27	-0.334	0.738
Pre-treatment TG (mmol/L)	1.79±0.73	1.81±0.65	1.78±0.79	-0.316	0.753
Pre-treatment TC (mmol/L)	4.88 [4.51, 5.38]	4.86 [4.48, 5.41]	4.88 [4.51, 5.33]	0.519	0.604
Pre-treatment LDL-C (mmol/L)	2.81±0.37	2.80±0.37	2.82±0.37	0.602	0.547
Pre-treatment HDL-C (mmol/L)	1.22±0.31	1.24±0.32	1.21±0.29	-0.65	0.516
Pre-treatment bone density (g/cm^2)	0.83±0.13	0.82±0.13	0.84±0.13	1.039	0.3
Pre-treatment cortisol (nmol/L)	261.05±115.54	259.23±109.23	262.64±121.20	0.228	0.82
Pre-treatment ACTH (pg/mL)	5.44 [3.20, 7.60]	5.59 [3.33, 7.59]	5.25 [2.83, 7.61]	0.577	0.564

Note: CAS, Clinical Activity Score; SIR, extraocular muscle average signal intensity ratio; FBG, fasting blood glucose; 2hPG, 2-hour postprandial glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACTH, adrenocorticotropic hormone.

lar muscle average signal intensity ratio (SIR, P=0.132), fasting blood glucose (FBG, P= 0.422), 2-hour postprandial glucose (2hPG, P=0.788), TG (P=0.157), TC (P=0.497), LDL-C (P=0.167), HDL-C (P=0.778), bone density (P=0.641), cortisol (P=0.435), and adrenocorticotropic hormone (ACTH, P=0.738) demonstrated no significant differences (**Table 2**).

Post-treatment ocular and metabolic indicators comparison

Post-treatment comparisons between groups revealed no significant differences across measured indicators. CAS (P=0.090), right eye exophthalmos (P=0.753), left eye exophthalmos (P=0.718), right extraocular muscle average diameter (P=0.604), left extraocular muscle average diameter (P=0.780), extraocular muscle average SIR (P=0.547), FBG (P=0.723), 2hPG (P=0.516), TG (P=0.581), TC (P=0.300), LDL-C (P=0.545), HDL-C (P=0.820), bone density (P=0.935), cortisol (P=0.564), and ACTH (P=0.977) showed no significant differences (**Table 3**).

Within-group pre- and post-treatment indicator comparison

High-dose group analysis revealed significant post-treatment improvements in CAS (P<0.001), right eye exophthalmos (P<0.001), left eye exophthalmos (P=0.006), left extraocular muscle average diameter (P=0.002), extraocular muscle average SIR (P=0.009), 2hPG (P=0.020), TG (P=0.022), TC (P=0.017), and HDL-C (P=0.028). Right extraocular muscle average diameter (P=0.269), FBG (P=0.718), LDL-C (P=0.143), bone density (P=0.728), cortisol (P=0.541), and ACTH (P=0.823) remained unchanged (**Table 4**).

Low-dose group analysis showed significant post-treatment changes in CAS (P<0.001), right eye exophthalmos (P=0.009), left eye exophthalmos (P<0.001), 2hPG (P<0.001), TC (P=0.001), and HDL-C (P=0.007). Right extraocular muscle average diameter (P=0.784), left extraocular muscle average diameter (P=0.590), extraocular muscle average SIR (P=0.272), FBG (P=0.346), TG (P=0.195), LDL-C (P=0.739), bone density (P=0.161), cortisol (P=0.532), and ACTH (P=0.579) showed no significant changes (**Table 5**).

Treatment efficacy comparison

High-dose and low-dose groups demonstrated comparable treatment effectiveness. Cure rates (P=0.887) and overall response rates (P=0.463) showed no statistical differences between treatment regimens (**Table 6**).

Diplopia outcomes comparison

Significant differences in diplopia improvement were observed between groups. Overall improvement rates were significantly higher in

Table 3. Comparison of post-treatment ocular and metabolic indicators between high-dose and low-dose groups

Variable	Total	High-dose group (n=112)	Low-dose group (n=128)	Test statistic	*P* value
Post-treatment CAS score (points)	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	0.314	0.753
Post-treatment right exophthalmos (mm)	18.18±2.32	18.22±2.16	18.14±2.47	-0.253	0.8
Post-treatment left exophthalmos (mm)	18.04±2.34	18.28±2.19	17.82±2.45	-1.51	0.132
Post-treatment right extraocular muscle average diameter (mm)	5.21 [4.90, 5.62]	5.21 [4.99, 5.51]	5.22 [4.75, 5.77]	0.269	0.788
Post-treatment left extraocular muscle average diameter (mm)	5.26±0.62	5.29±0.45	5.23±0.73	-0.68	0.497
Post-treatment extraocular muscle average SIR	1.66±0.26	1.66±0.29	1.67±0.23	0.282	0.778
Post-treatment FBG (mmol/L)	4.57±0.55	4.60±0.55	4.54±0.54	-0.782	0.435
Post-treatment 2hPG (mmol/L)	5.46 [4.02, 7.12]	5.64 [4.13, 7.51]	5.30 [3.97, 6.47]	1.695	0.09
Post-treatment TG (mmol/L)	1.64±0.58	1.63±0.55	1.66±0.60	0.362	0.718
Post-treatment TC (mmol/L)	4.63±0.86	4.65±0.88	4.61±0.86	-0.28	0.78
Post-treatment LDL-C (mmol/L)	2.85±0.40	2.86±0.35	2.84±0.45	-0.354	0.723
Post-treatment HDL-C (mmol/L)	1.32±0.27	1.33±0.28	1.31±0.27	-0.553	0.581
Post-treatment bone density (g/cm^2)	0.82±0.10	0.83±0.10	0.82±0.11	-0.606	0.545
Post-treatment cortisol (nmol/L)	268.63 [198.21, 332.24]	270.22 [188.44, 333.01]	267.17 [200.48, 331.26]	0.082	0.935
Post-treatment ACTH (pg/mL)	5.44 [3.44, 7.42]	5.22 [3.41, 7.79]	5.61 [3.45, 7.26]	0.029	0.977

Note: CAS, Clinical Activity Score; SIR, extraocular muscle average signal intensity ratio; FBG, fasting blood glucose; 2hPG, 2-hour postprandial glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACTH, adrenocorticotropic hormone.

Table 4. Within-group comparison of pre- and post-treatment ocular and metabolic indicators in high-dose group

Variable	High-dose group (n=112)		Test statistic	*P* value
	Pre-treatment	Post-treatment		
CAS score (points)	3.00 [3.00, 4.00]	2.00 [2.00, 3.00]	-7.256	<0.001
Right exophthalmos (mm)	19.19±2.60	18.22±2.16	2.978	0.004
Left exophthalmos (mm)	19.10±2.28	18.28±2.19	2.799	0.006
Right extraocular muscle average diameter (mm)	5.39±0.91	5.21 [4.99, 5.51]	-1.221	0.222
Left extraocular muscle average diameter (mm)	5.01±0.80	5.29±0.45	-3.162	0.002
Extraocular muscle average SIR	1.76±0.30	1.66±0.29	2.751	0.007
FBG (mmol/L)	4.57±0.62	4.60±0.55	-0.373	0.71
2hPG (mmol/L)	6.27±1.40	5.64 [4.13, 7.51]	-2.323	0.02
TG (mmol/L)	1.81±0.65	1.63±0.55	2.317	0.022
TC (mmol/L)	4.86 [4.48, 5.41]	4.65±0.88	-2.383	0.017
LDL-C (mmol/L)	2.80±0.37	2.86±0.35	-1.475	0.143
HDL-C (mmol/L)	1.24±0.32	1.33±0.28	-2.224	0.028
Bone density (g/cm^2)	0.82±0.13	0.83±0.10	-0.349	0.728
Cortisol (nmol/L)	259.23±109.23	270.22 [188.44, 333.01]	-0.613	0.541
ACTH (pg/mL)	5.59 [3.33, 7.59]	5.22 [3.41, 7.79]	0.224	0.823

Note: CAS, Clinical Activity Score; SIR, extraocular muscle average signal intensity ratio; FBG, fasting blood glucose; 2hPG, 2-hour postprandial glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACTH, adrenocorticotropic hormone.

Table 5. Within-group comparison of pre- and post-treatment ocular and metabolic indicators in low-dose group

Variable	Low-dose group (n=128)		Test statistic	*P* value
	Pre-treatment	Post-treatment		
CAS score (points)	3.00 [3.00, 4.00]	2.00 [2.00, 3.00]	-8.16	<0.001
Right exophthalmos (mm)	18.96±2.33	18.14±2.47	2.636	0.009
Left exophthalmos (mm)	19.27±2.04	17.82±2.45	5.184	P<0.001
Right extraocular muscle average diameter (mm)	5.29±1.03	5.22 [4.75, 5.77]	0.278	0.781
Left extraocular muscle average diameter (mm)	5.17±0.96	5.23±0.73	-0.54	0.59
Extraocular muscle average SIR	1.71±0.31	1.67±0.23	1.162	0.247
FBG (mmol/L)	4.60±0.64	4.54±0.54	0.866	0.388
2hPG (mmol/L)	6.21±1.27	5.30 [3.97, 6.47]	4.539	P<0.001
TG (mmol/L)	1.78±0.79	1.66±0.60	1.304	0.195
TC (mmol/L)	4.88 [4.51, 5.33]	4.61±0.86	3.356	0.001
LDL-C (mmol/L)	2.82±0.37	2.84±0.45	-0.334	0.739
HDL-C (mmol/L)	1.21±0.29	1.31±0.27	-2.736	0.007
Bone density (g/cm^2)	0.84±0.13	0.82±0.11	1.409	0.161
Cortisol (nmol/L)	262.64±121.20	267.17 [200.48, 331.26]	0.624	0.532
ACTH (pg/mL)	5.25 [2.83, 7.61]	5.61 [3.45, 7.26]	0.555	0.579

Note: CAS, Clinical Activity Score; SIR, extraocular muscle average signal intensity ratio; FBG, fasting blood glucose; 2hPG, 2-hour postprandial glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACTH, adrenocorticotropic hormone.

the high-dose group compared to the low-dose group (P=0.009), while the proportions with unchanged diplopia were significantly higher in the low-dose group (P=0.001) (**Table 7**).

Adverse event comparison

Treatment groups exhibited significant differences in adverse event profiles. Liver function

Table 6. Comparison of treatment efficacy between high-dose and low-dose groups

Group	Cured	Markedly effective	Effective	Ineffective	Overall response rate
High-dose group (n=112)	5 (4.46%)	36 (32.14%)	40 (35.72%)	31 (27.68%)	81 (72.32%)
Low-dose group (n=128)	6 (4.68%)	44 (34.37%)	37 (28.93%)	41 (32.03%)	87 (67.97%)
Test statistic		-0.142			0.539
P value		0.887			0.463

Table 7. Comparison of diplopia status between high-dose and low-dose groups

Group	Improved	Unchanged	Worsened	Overall improvement rate
High-dose group (n=112)	49 (43.75%)	56 (50.00%)	7 (6.25%)	49 (43.75%)
Low-dose group (n=128)	31 (24.22%)	92 (71.88%)	5 (3.90%)	31 (24.22%)
Test statistic		-5.942		10.254
P value		0.009		0.001

Table 8. Comparison of adverse reactions between high-dose and low-dose groups

Group	BMI increase	Hypertension	Liver dysfunction	Electrolyte disturbance	Sleep disorder	Total incidence
High-dose group (n=112)	8 (7.14%)	4 (3.57%)	20 (17.86%)	5 (4.46%)	3 (2.68%)	40 (35.71%)
Low-dose group (n=128)	2 (1.56%)	5 (3.91%)	4 (3.13%)	2 (1.56%)	2 (1.56%)	15 (11.72%)
Test statistic	3.366	0.042	12.814	0.899	0.023	19.470
P value	0.066	0.838	0.001	0.343	0.880	<0.001

Note: BMI, Body mass index.

impairment (P=0.001) and total adverse event incidence (P<0.001) were significantly higher in the high-dose group. BMI increases (P=0.066), hypertension (P=0.838), electrolyte disturbances (P=0.343), and sleep disorders (P=0.880) showed no significant between-group differences (**Table 8**).

Baseline characteristics between diplopia and non-diplopia patients

Diplopia and non-diplopia groups showed significant baseline differences in several indicators. Age (P<0.001), disease duration (P< 0.001), TRAb (P<0.001), pre-treatment CAS (P<0.001), pre-treatment extraocular muscle average SIR (P<0.001), treatment regimen (P=0.001), and smoking history (P=0.001) differed significantly between groups. Patients with diplopia had higher age, longer disease duration, elevated TRAb levels, higher pre-treatment CAS scores, and increased SIR values. High-dose treatment was more prevalent in the diplopia group, while smoking was less common.

Other variables including BMI (P=0.329), blood pressure measurements, thyroid function indicators , exophthalmos measurements, muscle diameter assessments, metabolic indicators, and demographic factors showed no significant differences (P>0.05 for all) (**Table 9**).

ROC curve analysis for diplopia classification

ROC curve analysis determined optimal cut-off values for continuous variables significantly different between diplopia and non-diplopia patients. Age (AUC=0.638), disease duration (AUC=0.659), TRAb (AUC=0.638), pre-treatment CAS (AUC=0.631), and pre-treatment SIR (AUC=0.650) demonstrated moderate discriminative ability with cut-off values of 48 years, 10 years, 10.18 IU/L, 4 points, and 1.75, respectively. Youden indices and F1 scores were 0.275 and 0.464 (age), 0.317 and 0.464 (disease duration), 0.275 and 0.464 (TRAb), 0.287 and 0.475 (CAS), and 0.300 and 0.366 (SIR), respectively (**Figure 1**).

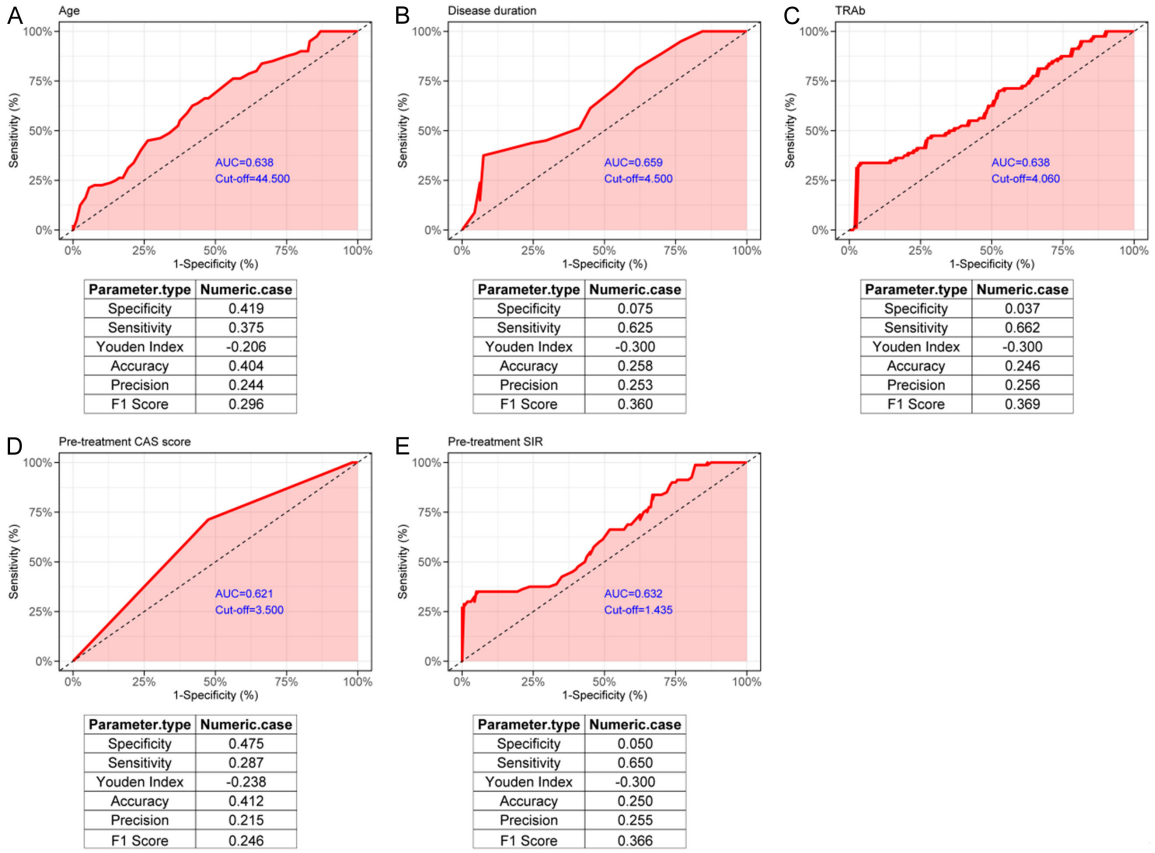
These continuous variables were converted to binary categories using identified optimal cut-off values for logistic regression modeling, improving clinical interpretability and enabling clearer risk stratification.

Table 9. Comparison of baseline characteristics and treatment regimens between diplopia and non-diplopia patients

Variable	Total	Diplopia (n=80)	Non-diplopia (n=160)	Test statistic	*P* value
Age (years)	45.00 [35.00, 54.25]	48.00 [38.00, 55.25]	41.00 [31.75, 49.00]	3.477	<0.001
BMI (kg/m^2)	24.20 [21.81, 26.36]	23.95 [21.68, 26.29]	24.69 [22.38, 26.62]	0.975	0.329
Disease duration (years)	9.00 [6.00, 12.00]	10.00 [7.00, 13.00]	8.00 [4.00, 11.00]	4.023	<0.001
Systolic BP (mmHg)	127.00 [122.75, 132.25]	128.00 [123.00, 132.00]	126.50 [121.75, 133.25]	0.229	0.819
Diastolic BP (mmHg)	77.19±6.25	76.88±6.28	77.80±6.19	-1.074	0.284
T3 (nmol/L)	1.85 [1.35, 2.42]	1.77 [1.29, 2.37]	2.01 [1.47, 2.61]	1.532	0.126
T4 (nmol/L)	103.45 [75.61, 126.72]	100.28 [77.05, 125.06]	103.95 [75.11, 126.78]	0.288	0.773
FT3 (pmol/L)	5.67±2.31	5.59±2.20	5.82±2.50	-0.747	0.456
FT4 (pmol/L)	17.40±6.62	17.57±6.55	17.04±6.80	0.583	0.560
TSH (mIU/L)	1.29 [0.83, 1.80]	1.27 [0.82, 1.78]	1.30 [0.92, 1.82]	0.222	0.824
TRAb (IU/L)	9.79 [5.78, 12.84]	10.18 [7.07, 13.38]	8.89 [3.25, 11.61]	3.478	<0.001
Pre-treatment CAS score (points)	3.00 [3.00, 4.00]	4.00 [3.00, 4.00]	3.00 [3.00, 4.00]	3.543	<0.001
Pre-treatment right exophthalmos (mm)	19.06±2.45	19.16±2.26	18.87±2.80	0.881	0.379
Pre-treatment left exophthalmos (mm)	19.19±2.15	19.00±2.07	19.58±2.28	-1.969	0.050
Pre-treatment right extraocular muscle average diameter (mm)	5.33±0.97	5.34±1.03	5.33±0.86	0.069	0.945
Pre-treatment left extraocular muscle average diameter (mm)	5.10±0.89	5.14±0.93	5.00±0.80	1.204	0.230
Pre-treatment extraocular muscle average SIR	1.73 [1.55, 1.95]	1.75 [1.57, 1.98]	1.68 [1.28, 1.85]	3.326	<0.001
Pre-treatment FBG (mmol/L)	4.59±0.63	4.57±0.63	4.63±0.64	-0.705	0.482
Pre-treatment 2hPG (mmol/L)	6.24±1.33	6.16±1.29	6.40±1.38	-1.337	0.183
Pre-treatment TG (mmol/L)	1.79±0.73	1.75±0.73	1.88±0.70	-1.275	0.204
Pre-treatment TC (mmol/L)	4.88 [4.51, 5.38]	4.88 [4.51, 5.36]	4.88 [4.54, 5.47]	0.153	0.879
Pre-treatment LDL-C (mmol/L)	2.81±0.37	2.84±0.34	2.75±0.41	1.799	0.073
Pre-treatment HDL-C (mmol/L)	1.22±0.31	1.23±0.31	1.22±0.31	0.114	0.909
Pre-treatment bone density (g/cm^2)	0.83±0.13	0.83±0.12	0.84±0.14	-0.895	0.372
Pre-treatment cortisol (nmol/L)	261.05±115.54	259.14±118.71	264.88±109.55	-0.362	0.718
Pre-treatment ACTH (pg/mL)	5.44 [3.20, 7.60]	5.30 [2.80, 7.30]	5.94 [3.75, 7.63]	1.732	0.083
Treatment regimen				10.254	0.001
High-dose	112 (46.67%)	49 (61.25%)	63 (39.38%)		
Low-dose	128 (53.33%)	31 (38.75%)	97 (60.62%)		
Gender				0.408	0.523
Male	119 (49.58%)	42 (52.50%)	77 (48.12%)		
Female	121 (50.42%)	38 (47.50%)	83 (51.88%)		
Smoking history				10.804	0.001
Yes	72 (30.00%)	13 (16.25%)	59 (36.88%)		
No	168 (70.00%)	67 (83.75%)	101 (63.12%)		

Alcohol consumption				0.735	0.391
Yes	40 (16.67%)	11 (13.75%)	29 (18.12%)		
No	200 (83.33%)	69 (86.25%)	131 (81.88%)		
Diabetes history				0.086	0.769
Yes	26 (10.83%)	8 (10.00%)	18 (11.25%)		
No	214 (89.17%)	72 (90.00%)	142 (88.75%)		
Marital status				1.539	0.215
Married	217 (90.42%)	75 (93.75%)	142 (88.75%)		
Other	23 (9.58%)	5 (6.25%)	18 (11.25%)		

Note: BMI, Body mass index; T3, triiodothyronine; T4, thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TRAb, thyrotropin receptor antibody; CAS, Clinical Activity Score; SIR, extraocular muscle average signal intensity ratio; FBG, fasting blood glucose; 2hPG, 2-hour postprandial glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACTH, adrenocorticotropic hormone.



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Specificity	0.419
Sensitivity	0.375
Youden Index	-0.206
Accuracy	0.404
Precision	0.244
F1 Score	0.296

Parameter.type	Numeric.case
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Sensitivity	0.625
Youden Index	-0.300
Accuracy	0.258
Precision	0.253
F1 Score	0.360

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Accuracy	0.246
Precision	0.256
F1 Score	0.369

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Accuracy	0.412
Precision	0.215
F1 Score	0.246

Parameter.type	Numeric.case
Specificity	0.050
Sensitivity	0.650
Youden Index	-0.300
Accuracy	0.250
Precision	0.255
F1 Score	0.366

Figure 1. ROC curve analysis. A. Age: Shows the ROC curve for age variable, evaluating its ability to predict diplopia. B. Disease duration: Shows the ROC curve for disease duration variable, assessing its correlation with diplopia. C. Thyrotropin receptor antibody (TRAb): Shows the ROC curve for TRAb levels, analyzing its ability to distinguish between diplopia and non-diplopia patients. D. Pre-treatment Clinical Activity Score (CAS): Shows the ROC curve for pre-treatment CAS score, evaluating its predictive value. E. Pre-treatment extraocular muscle average signal intensity ratio (SIR): Shows the ROC curve for pre-treatment SIR, assessing its discriminative ability. Note: AUC, Area under the curve; TRAb, thyrotropin receptor antibody; CAS, Clinical Activity Score; SIR, extraocular muscle average signal intensity ratio.

logistic regression analysis of diplopia risk

Variable selection for multivariate modeling followed structured methodology. Clinically relevant variables from previous TAO studies underwent univariate screening, with ROC analysis determining discriminatory power and optimal cut-off values. Variables with established clinical significance were retained despite relatively low Youden indices to adjust for confounding effects, while indicators not improving model performance were excluded to prevent overfitting.

Univariate analysis identified significant diplopia risk associations: treatment regimen (P=0.002, OR=2.434), age (P=0.003, OR=0.432), disease duration (P<0.001, OR=0.135), TRAb (P<0.001, OR=0.076), pre-treatment CAS (P<0.001, OR=0.365), pre-treatment extraocular muscle average SIR (P<0.001, OR=0.098), and smoking history (P=0.001, OR=0.332).

Multivariate analysis revealed that compared to high-dose treatment, low-dose patients had increased non-diplopia risk post-treatment (P<0.001, OR=6.141). Longer disease duration (P<0.001, OR=0.062), higher TRAb levels (P<0.001, OR=0.053), higher pre-treatment SIR (P<0.001, OR=0.058), and smoking history (P=0.044, OR=0.397) were associated with decreased diplopia probability. Age and pre-treatment CAS showed no significant associations (P>0.05) (**Figure 2**).

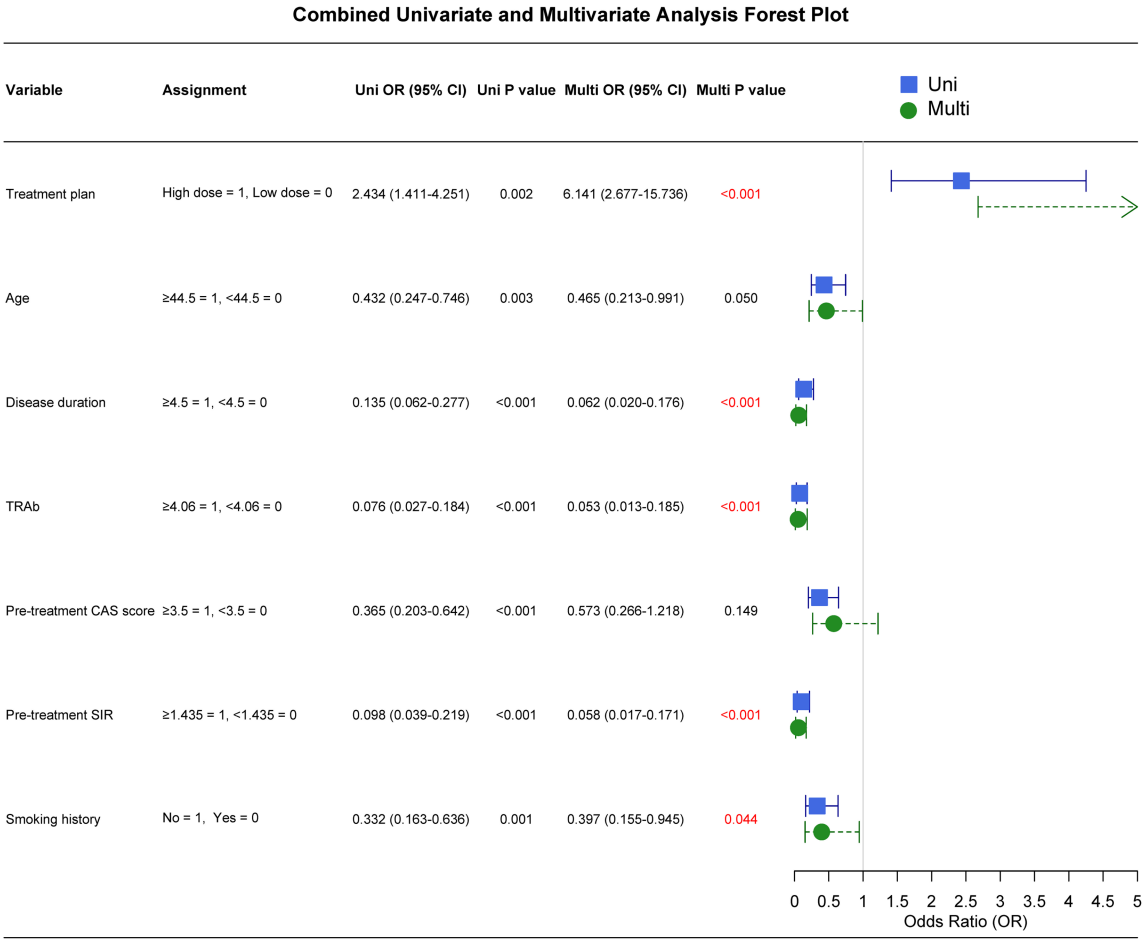


Figure 2. Forest plot of univariate and multivariate logistic regression analysis. Note: OR, Odds ratio; TRAb, thyrotropin receptor antibody; CAS, Clinical Activity Score; SIR, extraocular muscle average signal intensity ratio.

IPWT-weighted logistic regression analysis

IPWT-weighted analysis adjusting for age and disease duration confirmed similar risk factor patterns. Univariate analysis identified significant associations with treatment regimen (P<0.001, OR=2.631), age (P=0.004, OR=0.45), disease duration (P<0.001, OR=0.123), TRAb (P<0.001, OR=0.085), pre-treatment CAS (P<0.001, OR=0.359), pre-treatment extraocular muscle average SIR (P<0.001, OR=0.089), and smoking history (P=0.002, OR=0.352).

Multivariate analysis showed low-dose patients had increased non-diplopia risk (P<0.001, OR=6.031), while longer disease duration (P<0.001, OR=0.061), higher TRAb levels (P<0.001, OR=0.062), and higher pre-treatment SIR (P<0.001, OR=0.057) decreased diplopia probability. Smoking, age, and pre-treatment CAS showed no significant associations (P>0.05) (**Figure 3**).

Discussion

Intravenous glucocorticoid pulse therapy has gained widespread recognition in TAO treatment, yet dosing strategy controversies have become increasingly prominent. Aishwarya et al. [15] noted in their systematic review that moderate-dose (4.5 g) regimens represent the most commonly adopted treatment approach, significantly improving clinical activity scores and quality of life while demonstrating relatively fewer side effects. The European Thyroid Association favors conservative 8 g cumulative dose limits, while American treatment strategies show greater flexibility. Most clinical studies pursue efficacy data but provide insufficient attention to metabolic consequences during

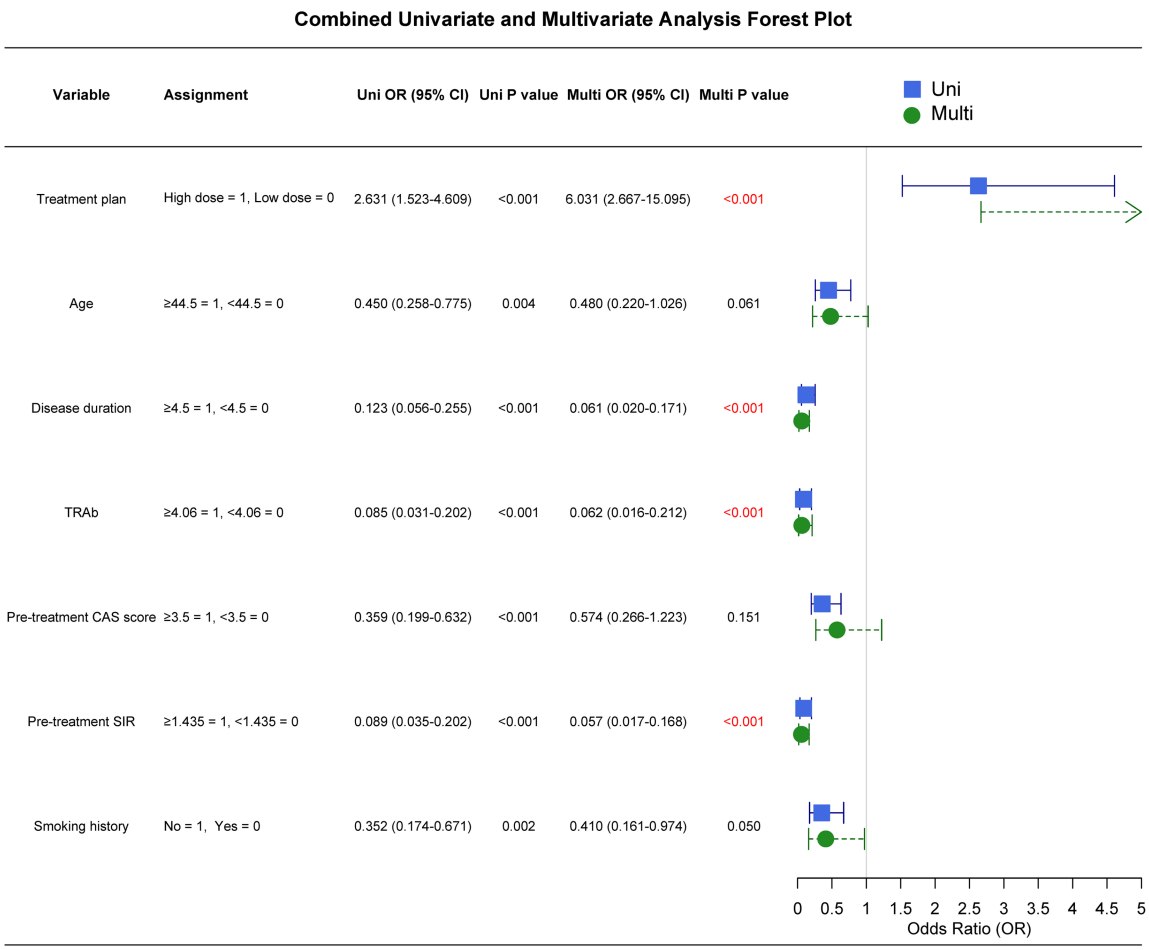


Figure 3. Forest plot of IPWT-weighted univariate and multivariate logistic regression analysis. Note: OR, Odds ratio; TRAb, thyrotropin receptor antibody; CAS, Clinical Activity Score; SIR, extraocular muscle average signal intensity ratio; IPWT, inverse probability weighting technique.

treatment. Literature indicates [16] that 4.5-5 g cumulative dose intravenous glucocorticoid pulse therapy appears optimal for both efficacy and safety.

While both treatment regimens demonstrated good efficacy in controlling TAO inflammatory activity, detailed differences revealed dose selection complexity. High-dose regimens showed particularly outstanding efficacy performance, closely related to the classic dose-response relationship of glucocorticoids. Liu et al. [10] prospectively validated the effectiveness, safety, and good tolerability of high-dose intravenous glucocorticoid pulse therapy with relatively mild side effects. Regarding exophthalmos improvement, the high-dose group demonstrated an average reduction of 2.3 mm compared to 1.6 mm in the low-dose group. This significant difference represented clinically meaningful improvement for patients.

Chen et al. [17] demonstrated that higher extraocular muscle water content better predicts methylprednisolone pulse therapy (MPPT) efficacy, providing evidence for imaging-based treatment response assessment. This difference may relate to high-dose glucocorticoids' deeper intervention in inflammatory cascade reactions. Through potent phospholipase A2 activity inhibition, high-dose regimens more thoroughly block arachidonic acid metabolic pathways, reducing inflammatory mediator generation including prostaglandins and leukotrienes [18]. Simultaneously, high-dose glucocorticoids demonstrate more significant stabilizing effects on cellular and lysosomal mem-

branes, effectively controlling abnormal release of vasoactive substances like histamine [19].

Despite high-dose treatment demonstrating significant efficacy, metabolic risks cannot be ignored. Literature reports [20] indicate that 12-week intravenous glucocorticoid pulse therapy may lead to glucocorticoid-induced adrenal insufficiency, therefore recommending careful adrenal function assessment after treatment.

For patients with glucocorticoid-resistant or intolerant conditions, alternative treatment approaches have demonstrated good efficacy. Muller et al. [21] reported successful treatment of hormone-resistant moderate-to-severe thyroid eye disease (TED) patients with rituximab, achieving good results with single 500 mg intravenous injection. Similarly, literature indicates [22] that tocilizumab as second-line treatment significantly improves clinical outcomes and quality of life in glucocorticoid-resistant moderate-to-severe Graves' ophthalmopathy (GO) patients.

Additionally, Stoynova et al. [23] demonstrated that orbital radiotherapy combined with low-dose glucocorticoids achieves good treatment responses in moderate-to-severe active GO, providing additional options for individualized treatment regimens.

Diplopia symptom improvement differences (36.6% vs 24.2%) reflect the pathophysiological basis of extraocular muscle dysfunction. High-dose glucocorticoids effectively inhibit excessive fibroblast proliferation and collagen over-synthesis, thereby preventing pathological fibrosis processes in extraocular muscles. Giannakogeorgou et al. [24] found that smoking, diplopia, and age were negative factors for avoiding surgery, while visual impairment was a favorable factor, providing predictive evidence for individualized treatment.

However, metabolic consequences remain concerning. Significant differences in liver function impairment (17.86% vs 3.13%) exposed potential risks of high-dose regimens. Literature indicates [25] that high-dose intravenous glucocorticoid treatment may trigger serious hepatic complications such as autoimmune hepatitis.

Bone metabolism safety data also warrant attention. Harsløf et al. [26] found that bone turnover decreased and bone structure improved during 12-week high-dose methylprednisolone treatment, considering intravenous glucocorticoid pulse therapy relatively safe from bone health perspectives. However, Rymuza et al. [27] and other studies [28] found that intravenous glucocorticoid pulse therapy may be associated with decreased bone formation and resorption and bone microstructure loss, suggesting a need for osteoporosis clinical risk factor assessment before treatment.

SIR as an imaging biomarker holds important value in disease assessment. Higher SIR indicates more significant extraocular muscle inflammatory edema. Such patients, although having more severe baseline conditions, have pathologic changes mainly characterized by reversible inflammation, therefore usually showing good responsiveness to glucocorticoid treatment. This characteristic contrasts sharply with patients whose main manifestations are irreversible fibrosis.

Surgery-related studies provide supplementary evidence for diplopia risk factor identification. Stähr et al. [29] found in studies of new-onset diplopia after orbital decompression surgery that medial rectus diameter enlargement, abduction and upward rotation dysfunction, and significant exophthalmos reduction were independent risk factors, consistent with baseline anatomic characteristics' effect on diplopia risk.

Multicenter predictive model studies [30] further demonstrated that age, clinical activity scores, and extraocular muscle-to-orbital area ratios serve as important indicators for predicting postoperative diplopia occurrence, providing references for multidimensional diplopia risk assessment. Laezza et al. [31] showed that glucocorticoid treatment history does not affect strabismus surgery success rates in thyroid-associated ophthalmopathy patients, but patients with previous orbital decompression surgery often require more surgical interventions to correct diplopia.

Treatment regimen selection played a crucial role in diplopia treatment effectiveness. Multivariate analysis indicated that compared to high-dose treatment, low-dose patients had significantly increased diplopia treatment failure risk (OR=6.031, P<0.001). This result

emphasizes the significant advantages of high-dose intravenous glucocorticoid pulse therapy in improving extraocular muscle dysfunction. High-dose regimens more effectively inhibit excessive fibroblast proliferation and collagen over-synthesis, more thoroughly control inflammatory cascade reactions, thereby demonstrating superior performance in diplopia symptom improvement and maintenance.

Regarding age and pre-treatment CAS scores, although univariate analysis showed significant associations with diplopia treatment effectiveness, they lost statistical significance in multivariate analysis using IPWT correction methods. This suggests these factors have limited independent impact on diplopia treatment effectiveness after balancing other confounding variables. Age factors may indirectly affect treatment effectiveness by influencing tissue repair capacity and drug metabolism, but their effects may be masked by other more specific factors. As a comprehensive indicator of disease activity, CAS score effects may be replaced by more objective and specific imaging indicators like SIR, reflecting the important value of imaging examinations in disease assessment.

Smoking research results require special attention. Univariate analysis showed smoking had significant statistical significance (P= 0.002, OR=0.352), suggesting it might be a protective factor for successful diplopia treatment. However, by multivariate analysis, smoking's *P*-value was exactly 0.05, the statistical significance threshold, indicating this factor remains at the borderline of statistical significance after adjusting for other variables, with its influence possibly real but relatively weak.

This result contrasts with existing literature recognizing smoking as an adverse prognostic factor for TAO. Possible explanations include selection bias, insufficiently adjusted confounding factors, or sample size limitations. Given the *P*-value at the critical point, clinical practice should continue adhering to existing evidence-based medical evidence, continuing to emphasize smoking cessation importance for TAO patients.

This study employed IPWT correction methods, effectively balancing baseline differences between groups and reducing selection bias impact. Post-correction result consistency enhanced conclusion robustness, providing more reliable evidence for clinical decision-making. Establishing such multifactorial risk prediction models provides scientific evidence for individualized TAO patient treatment strategy development, helping clinicians more accurately assess patient diplopia risk before treatment, thereby selecting the most appropriate treatment regimens.

This study has certain limitations. The retrospective study design's inherent limitations represent challenges we must acknowledge. Selection bias and information bias may affect result accuracy, as patient baseline characteristics and treatment choices may have systematic differences. The 4-week follow-up period limitation cannot be ignored, as we cannot observe long-term treatment effects, particularly glucocorticoid long-term metabolic impacts and TAO recurrence risks. Single-center study limitations further constrain result generalizability.

Future research blueprints should be more comprehensive and systematic. Multicenter, large-sample prospective randomized controlled trials represent the gold standard, and establishing long-term follow-up cohorts - beyond the 4-week period of this study-will be essential to fully evaluate the sustained metabolic effects of glucocorticoid therapy and the risk of TAO recurrence. In addition, prospective validation of SIR values and TRAb levels as predictive biomarkers for treatment response should be prioritized, as suggested by the trends observed in this study. Investigating adjunctive strategies, such as combining glucocorticoids with hypoglycemic or lipid-lowering agents, could help mitigate the metabolic risks identified here. Individualized treatment strategy exploration, biomarker discovery, and combination therapy optimization all warrant in-depth research. For patients who respond poorly to or cannot tolerate glucocorticoids, the potential of biological agents such as rituximab and tocilizumab, as well as optimized orbital radiotherapy combination regimens, should also be further investigated.

Conclusion

This study underscored the balance between efficacy and metabolic safety in TAO treatment.

High-dose regimens provided stronger early improvements, especially in patients with more active inflammation (elevated SIR/TRAb), whereas low-dose regimens may be preferable for those with higher metabolic risk. Physicians should tailor dosing strategies according to baseline disease activity and metabolic profiles to optimize outcomes.

Disclosure of conflict of interest

None.

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