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Journal

Ophthalmic Plastic and Reconstructive Surgery, 38(6)

ISSN

0740-9303

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Publication Date

2022-11-01

DOI

10.1097/iop.0000000000002196

Predictive Modeling of New-Onset Postoperative Diplopia Following Orbital Decompression for Thyroid Eye Disease

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Purpose: To identify risk factors for the development of new-onset, postoperative diplopia following orbital decompression surgery based on patient demographics, clinical exam characteristics, radiographic parameters, and surgical techniques.

Methods: We conducted a multi-center retrospective chart review of patients who underwent orbital decompression for thyroid eye disease (TED). Patient demographics, including age, gender, smoking history, preoperative exophthalmometry, clinical activity score (CAS), use of peribulbar and/or systemic steroids, and type of orbital decompression were reviewed. Postoperative diplopia was determined at a minimum of 3 months postoperatively and before any further surgeries. Cross-sectional area ratios of each extraocular muscle to orbit and total fat to orbit were calculated from coronal imaging in a standard fashion. All measurements were carried out using PACS imaging software. Multivariable logistic regression modeling was performed using Stata 14.2 (StataCorp, College Station, TX).

Results: A total of 331 patients without preoperative diplopia were identified. At 3 months postoperatively, 249 patients had no diplopia whereas 82 patients developed diplopia. The average postoperative follow-up was 22 months (range 3–156) months. Significant preoperative clinical risk factors for postoperative diplopia included older age at surgery, proptosis, use of peribulbar or systemic steroids, elevated clinical activity score, and presence of preoperative compressive optic neuropathy. Imaging findings of enlarged cross-sectional areas of each rectus muscle to the overall orbital area also conferred a significant risk of postoperative diplopia. Regarding surgical factors, postoperative diplopia was more common among those undergoing medial wall decompression, bilateral orbital surgery, and balanced decompression, whereas endoscopic medial wall decompression was found to be relatively protective.

Conclusions: This study identifies risk factors associated with the development of diplopia following orbital decompression using multivariable data. This study demonstrates that several characteristics including age, clinical activity score, the cross-sectional muscle to orbit ratios, in addition to the type of orbital decompression surgery, are predictive factors for the development of new-onset postoperative diplopia.

(*Ophthalmic Plast Reconstr Surg* 2022;38:551–557)

The clinical manifestations of thyroid eye disease (TED) can range from mild to devastating, due to a cascade of orbital and soft tissue changes that occur within the periocular region.[1] Proptosis, restrictive strabismus, periorbital soft tissue changes, exposure keratopathy, and optic neuropathy can result in pain, double vision, corneal scarring, and irreversible vision loss. These are some of the more incapacitating sequelae of the autoimmune process, which typically exhibits an active process for 1–3 years, followed by a quiescent phase.[1,2] The clinical activity score (CAS) is one system used to grade disease activity.[3] Biologically, TED is characterized by lymphocytic infiltration and fibroblast activation. These processes lead to adipogenesis, and the production and deposition of glycosaminoglycans within extraocular muscles, the intermuscular septations, and the orbital fat compartment, leading to hyperosmotic forces that worsen edema.[1] A different subset of individuals, however, can exhibit a form of "fat-predominant" disease comprised mainly of enlargement of the orbital fat.[4]

Accepted for publication March 9, 2022.

Supported by the Bell Charitable Foundation, Rancho Santa Fe, CA; Research to Prevent Blindness, New York, NY.

D.O.K. and B.S.K. Consultant for Horizon Therapeutics. The other authors have no conflicts of interest to disclose.

A.A.N., and L.S.E. contributed equally to this article.

Presented at ASOPRS 49th Annual Fall Scientific Symposium, Chicago, October 25,26, 2018.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.op-rs.com).

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DOI: 10.1097/IOP.0000000000002196

Overall, TED more commonly affects women and those with hyperthyroidism.[2,5] TED tends to occur along a bimodal age distribution with a more severe clinical course associated with increasing age, prior smoking history, and the male gender.[6] Medical treatment options include corticosteroids, orbital radiotherapy, B-cell depletion, and targeted biologic agents. Surgical decompression may be needed in urgent cases of vision loss due to compressive optic neuropathy or exposure keratopathy, or in those with quiescent disease and persistent proptosis or symptomatic ocular exposure. The surgical approaches to orbital decompression vary between surgeons based on training and preferred practice patterns. Surgical approaches may include the lateral wall, the trans-nasal endoscopic medial wall, and floor, as well as transcaruncular and transconjunctival approaches to the medial orbit and floor.[7–14] Various combinations may be used to individualize proptosis reduction.

Diplopia, however, is a more common side effect of both the underlying disease process and/or orbital decompression. New-onset postoperative diplopia (NOPD) has been reported to occur in 3.8%–64% of patients undergoing orbital decompression.[15–18] This potential sequela, which is typically treatable with strabismus surgery, negatively affects the patient's quality of life.[19] Double vision can preclude essential functions such as driving and walking, and cause work disability. Prior studies have examined factors that influence the risk of NOPD, including the type or combination of decompression procedures performed.[6,15–17,20] These studies, however, are limited by small sample size, single institution or isolated surgeon practices, types of decompressions studied, and nonstandardized reporting of demographic and clinical data. Given the limitation and lack of prior guidance regarding NOPD, our multiinstitutional study aims to provide a predictive model to guide preoperative counseling and surgical planning.

METHODS

A multicenter retrospective chart review was performed of patients who underwent orbital decompression for TED during a 16-year-period from January 1, 2002 to October 1, 2017. Exclusion criteria were: age less than 18 years; prior radiation or surgical orbital decompression; presence of preoperative diplopia in primary position; less than 3 months of follow-up; and incomplete clinical data or imaging. Institutional review board approval was obtained from each institution's Human Research Protection Program. This study adhered to the ethical principles outlined in the Declaration of Helsinki Health Insurance Portability and Accountability Act compliance was maintained throughout the study.

Data collected included age, gender, smoking history, preoperative exophthalmometry, type of orbital decompression (i.e., lateral, medial, and/or floor decompression, endoscopic, fat decompression, strut preservation, or bilateral surgery), use of peribulbar and/or systemic steroids, and CAS at the initial visit. The patient was considered a smoker if they had smoked within 6 months of surgery. Orbital decompression was performed by 10 surgeons at 8 institutions using established techniques.[7] Postoperative diplopia was measured as a discrete binary variable and determined at a minimum of 3 months postoperatively and before any further surgery. Diplopia upon reading and the degree of change were not studied. The ratio of the cross-sectional area of each extraocular muscle to orbit and total fat to orbit was calculated at approximately 1.5 cm anterior to the superior orbital fissure on coronal CT. The following subsets of orbital fat percentage were established: 0: >75% fat, 1: 50%–75% fat, 2: 25%–50% fat, and 3: <25%. All measurements were carried out using imaging software (See Fig. 1). Statistical analyses were performed using Stata 14.2. Bivariate analyses of categorical and continuous variables were performed using chi-square and Wilcoxon rank-sum tests, respectively. A Bonferroni correction was used to account for multiple comparisons.

Multivariable logistic regressions and receiver operating characteristic (ROC) curves were generated for multiple logistic regression models. The area under the receiver operating characteristics (AUROC) was used to compare the various logistic regression models. All multi-institutional data were aggregated and analyzed by a single statistician, who was masked to the potential bias from a single surgeon and/or institution.

RESULTS

Three hundred thirty-one total patients and 563 orbits (229 bilateral, 105 unilateral) who did not have preoperative diplopia on primary gaze underwent orbital decompression from January 1, 2002 to October 1, 2017. The average follow-up was 21.9 months (range 3–156 months). Totally 172 individuals with preoperative diplopia were excluded.

Patient Demographics. The study identified 331 patients without preoperative diplopia, of whom 82 patients (24.8%) developed new postoperative diplopia in the primary position. Older age at the time of surgery was found to be statistically significant (51 vs. 48 years, $p = 0.017$) in developing NOPD (Table 1). Other variables, such as gender, history of prior radioactive iodine treatment, smoking history, and history of prior surgical thyroidectomy were not found to be statistically significant.

Preoperative Clinical Characteristics. The preoperative examination included measures of exophthalmometry, optic nerve function, diplopia, and CAS. A greater degree of proptosis (24.8 vs. 23.7 mm, $p = 0.047$), diagnosis of compressive optic neuropathy (27% vs. 11%, $p = 0.001$), and higher preoperative CAS score (2.3 vs. 1.6, $p \leq 0.001$) were found to be statistically significant in predicting NOPD (Table 1).

Preoperative Imaging Characteristics. In bivariate analysis, an enlarged cross-sectional area of each rectus muscle was predictive for developing NOPD, (inferior rectus 12.5 vs. 10.1, medial rectus 9.6 vs. 7.8, superior rectus 12.2 vs. 9.7, lateral rectus 12.5 vs. 10.4; each $p < 0.001$, see Table 2). It accordingly followed that a smaller total fat to orbital area ratio was also predictive of new-onset postoperative diplopia (low fat to orbit 48.4 vs. 55.9, $p < 0.001$, Table 2). Each of these values are reported as a percentage of the overall orbital cross-sectional area.

Perioperative Factors. All procedures were carried out by fellowship-trained oculoplastic surgeons using published techniques.[7] The use of peribulbar steroids (24% vs. 6%, $p < 0.001$), use of systemic steroids (48% vs. 30%, $p = 0.003$), bilateral surgery, i.e., both simultaneous and sequential surgery, (82% vs. 65%, $p = 0.004$), and balanced surgery (63% vs. 47%, $p = 0.01$) were all associated with significantly greater risk of developing NOPD. Endoscopic medial wall decompression was associated with less risk of diplopia (10.4% vs. 21.8%, $p = 0.028$). There was not enough power to assess the relationship of the endoscopic decompressions beyond a medial wall decompression. Floor and lateral wall surgery were not found to have any predictive value in NOPD (Table 3).

Multivariable Logistic Regression Analysis. Correlation coefficients were calculated for each of the cross-sectional area ratios. A moderate correlation ($r > 0.3$) was found between each of the individual muscles, and a significant correlation ($r > 0.7$) was found between the fat to orbit ratio and the cross-sectional areas of each of the individual muscles. A multivariable logistic regression model (Table 4, Fig. 2) was developed to predict NOPD using independent preoperative characteristics. Of note, there were not enough patients under 20 or over 80 years old to include in the analysis. In the multivariable model, an increased fat to orbit ratio, use of peribulbar steroids, strut preservation, bilateral surgery, and medial endoscopic surgery were each found to be independent risk factors for postoperative diplopia after orbital decompression for TED. An ROC curve of the logistic regression was completed with an AUROC of 0.79 (Fig. 3).

The following are examples illustrating how to apply the logistic regression model.

Probability estimation of postoperative diplopia (p) = $e^{a+bX}/[1 + e^{a+bX}]$

$p = e^{logit}/[1 + e^{logit}]$, where logit = a+bX

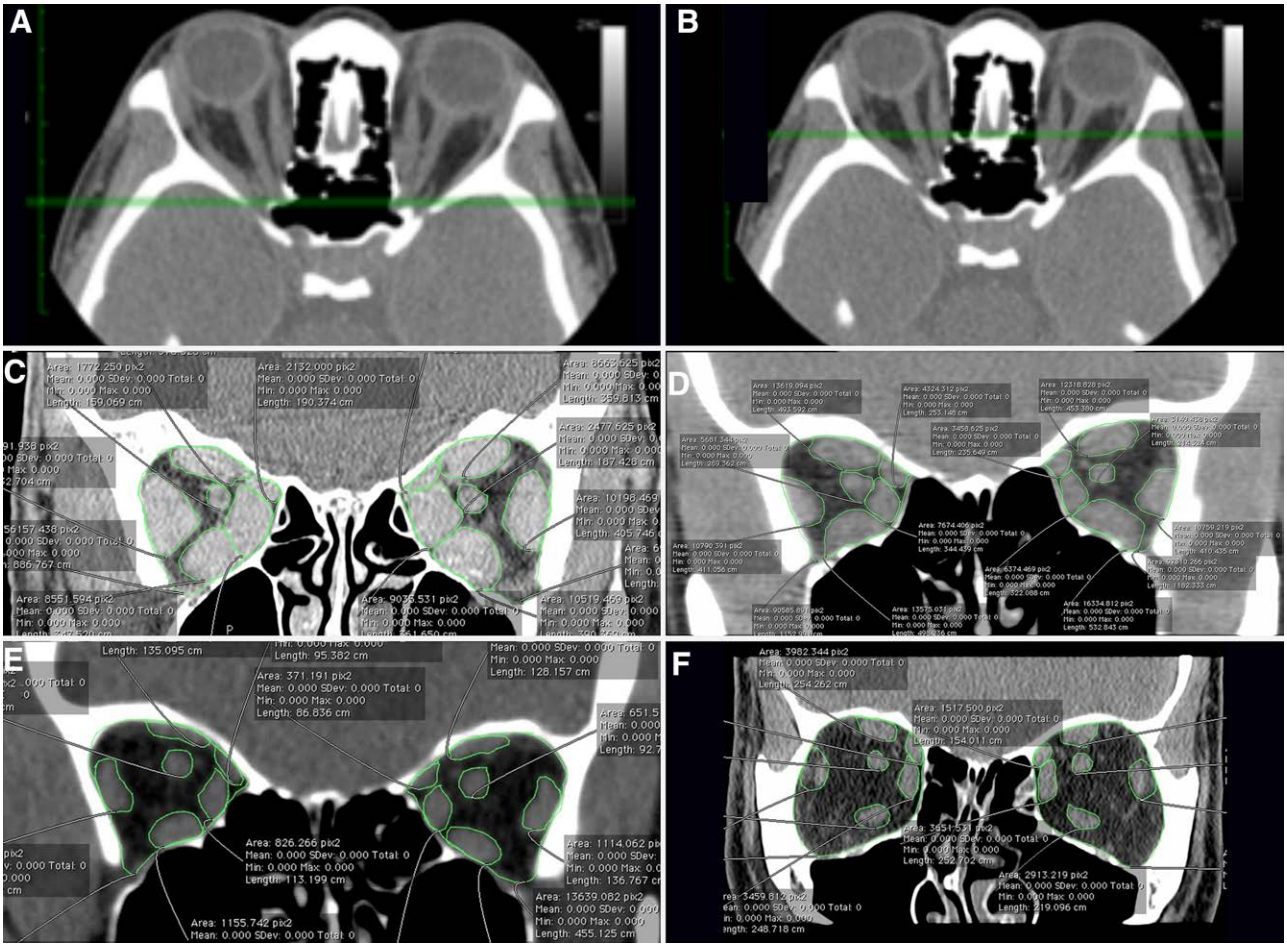

FIG. 1. Contouring analysis. Axial and coronal CT soft tissue images are linked within the viewer. In the axial plane, the anterior border of the superior orbital fissure (SOF) is identified as the initial reference point (**A,** horizontal green line). Next, a point 15 mm ± 2 mm anterior to the SOF in the axial plane is identified (**B,** horizontal green line). In the corresponding coronal image, extraocular muscles (EOMs) and optic nerves are manual traced for various fat to orbit ratios (**C**) >75% fat, (**D**) 50%–75%, (**E**) 25%–50%, and (**F**) <25%. All measurements were done using OsiriX Imaging Software. full color online

Logit output of developing diplopia (logit) = 1.06*a −1.36*b −0.60c −0.36*d −0.17*e + 0.27*f + 0.78 *g + 1.85*h −1.07*i −1.06*j +0.30 *k + 0.55*l + 0.36*m + 0.05*n −2.68

TABLE 1. Patient demographic and clinical characteristics

Variable	No post-op diplopia	Post-op diplopia	*p*
Total, n	249	82	
Age at surgery in years (SD)	47.5 (SD: 14.30)	51.2 (SD: 13.05)	0.017
Female (%)	80.3	75.6	0.362
Radioactive iodine history (%)	43.0	52.4	0.135
Surgical thyroidectomy (%)	13.8	22.0	0.078
Preoperative optic neuropathy (%)	10.9	26.6	0.001
Current or history of smoking in the last 6 months (%)	19.0	19.5	0.911
Postoperative follow-up (months)	18.8	31.1	<0.001
Exophthalmometry (mm)	23.7	24.8	0.047
CAS Score	1.64	2.28	<0.001

CAS, clinical activity score.
p: 2-sided and calculated by Wilcoxon Rank Sum for continuous variables or chi-square for binary variables.

Case 1. A 38-year-old female, never-smoker, with a history of Hashimoto's thyroiditis and stable thyroid eye disease presents with complaints of bulging eyes for over 5 years. Her discrete fat to orbit ratio is approximately 80% on neuroimaging review. She has never received systemic steroids. It is decided to pursue bilateral balanced 2 walls (medial wall and lateral wall) transorbital decompression with strut preservation without peribulbar steroid injections. Endoscopic surgery is not utilized.

Logit output of diplopia (logit) = 1.06**a* −1.36**b* −0.60*c* −0.36*d −0.17**e* + 0.27**f* + 0.78 **g* + 1.85**h* −1.07**i* −1.06**j* +0.30 **k* + 0.55**l* + 0.36**m* + 0.05**n* −2.68

a = 0 (>75% fat), b = 1 (20–40 years old), c = 0 (40–60 years), d = 0 (60–80 years), e = 1 (female), f = 0 (radioactive iodine), g = 1 (bilateral

TABLE 2. Preoperative imaging characteristics univariate analysis*

Variable	No post-op diplopia	Post-op diplopia	*p*
Inferior rectus (%)	10.1	12.5	<0.001
Medial rectus (%)	7.8	9.6	<0.001
Superior rectus (%)	9.7	12.2	<0.001
Lateral rectus (%)	10.4	12.5	<0.001
Fat to orbit, Low (%)	55.9	48.4	<0.001

*All values listed are listed as a percent of total cross-sectional area.

TABLE 3. Perioperative factors*

Variable	No post-op diplopia	Post-op diplopia	*p*
Deep lateral wall decompression (%)	62.2	69.5	0.235
Floor decompression (%)	61.1	67.9	0.270
Medial wall (%)	84.6	95.1	0.015
Endoscopic decompression (%)	20.2	9.9	0.035
Medial wall endoscopic (%)	21.76	10.39	0.028
Transorbital medial wall nonendoscopic (%)	78.24	89.61	0.028
Balanced (%)	47.0	63.4	0.010
Strut preservation	48.6	43.9	0.461
Bilateral surgery (%)*	64.7	81.7	0.004
3 wall decompression (%)	30.5	40.2	0.104
Peribulbar steroids (%)	6.43	24.4	<0.001
Systemic steroids (%)	29.6	47.6	0.003
Fat decompression (%)	75.8	69.5	0.259

*All values listed are listed as a percent of total cross-sectional area.

surgery), h = 0 (peribulbar steroids), i = 0 (medial endoscopic surgery), j = 1 (strut preservation), k = 1 (balanced decompression), l = 0 (floor decompression), m = 0 (systemic steroids), n = 0 (smoking history)

Logit output of diplopia (logit) =1.06*0 −1.36*1−0.60*0 −0.36*0 −0.17*1 + 0.27*0 + 0.78 *1 + 1.85*0 −1.07*0 −1.06*1 +0.30 *1 + 0.55*0 + 0.36*0 + 0.05*0−2.68

logit = −4.19

$p = e^{logit}/[1 + e^{logit}]$

Probability estimation of postoperative diplopia = 2%

Case 2. A 68-year-old female nonsmoker with quiescent thyroid eye disease presents for evaluation of significant bilateral proptosis. On CT review, her discrete fat to orbit ratio is approximately 20%. She has a history of prior systemic steroid treatment. It is decided to pursue bilateral balanced 2 walls (medial wall and lateral wall) transorbital decompression with strut preservation and peribulbar steroid injections. Endoscopic surgery is not utilized.

Logit output of diplopia (logit) = 1.06*a −1.36*b −0.60c −0.36*d −0.17*e + 0.27*f + 0.78 *g + 1.85*h −1.07*I −1.06*j +0.30 *k + 0.55*l + 0.36*m + 0.05*n −2.68

a = 3 (<25% fat), b = 0 (20–40 years old), c = 0 (40–60 years), d = 1 (60–80 years), e = 1 (female), f = 0 (radioactive iodine), g = 1 (bilateral surgery), h = 1 (peribulbar steroids), i = 0 (medial endoscopic surgery), j = 1 (strut preservation), k = 1 (balanced decompression), l = 0 (floor decompression), m = 1 (systemic steroids), n = 0 (smoking history)

Logit output of diplopia (logit) = 1.06*3 −1.36*0 −0.60*0 −0.36*1 −0.17*1 +0.27*0 +0.78*1 +1.85*1 −1.07*0 −1.06*1 +0.30*1 + 0.55*0 + 0.36*1 + 0.05*0−2.68

TABLE 4. Multivariable logistic regression analysis

Variable	Odds ratio	Coefficient	*p*
Fat to orbit ratio	2.87	1.06	<0.001
Age 20–40 years	0.26	−1.36	0.260
Age 40–60 years	0.55	−0.60	0.610
Age 60–80 years	0.70	−0.36	0.767
Female	0.84	−0.17	0.652
Radioactive iodine history	1.31	0.27	0.392
Bilateral surgery	2.19	0.78	0.043
Peribulbar steroid use	6.38	1.85	<0.001
Medial endoscopic	0.34	−1.07	0.024
Strut preservation	0.35	−1.06	0.014
Balanced decompression	1.35	0.30	0.427
Floor decompression	1.73	0.55	0.254
Systemic steroid use	1.43	0.36	0.308
Smoking history	1.05	0.05	0.897

logit = 2.2

$p = e^{logit}/[1 + e^{logit}]$

Probability estimation of postoperative diplopia = 88%

*For conversion table to convert logit output to probability estimation, see Tables 1 and 2, Supplemental Digital Content 1, http://links.lww.com/IOP/A334.

DISCUSSION

Preoperative counseling is essential to prepare patients for the potential of new-onset postoperative diplopia following orbital decompression surgery. The focus of this study is strictly on NOPD and excluded patients with preexisting or intermittent diplopia. Our bivariate analyses showed that older age, proptosis, higher clinical activity score, and compressive optic neuropathy were each associated with increased risk of NOPD if examined individually. While older age, smoking, and uncontrolled thyroid hormone levels have been associated with more severe disease,[1,2,5,6] we conclude that certain patient demographics and clinical characteristics also increase the risk of diplopia. Peribulbar and systemic steroid use are also correlated with increased risk of NOPD. This may be because patients with more clinically active diseases are often treated with steroids, confounding this result. Perioperative corticosteroids should therefore be given when clinically indicated. For example, the use of perioperative steroids have been shown to lead to improvement in CAS, and the reduction in the degree of eyelid retraction, rates of strabismus, and amount of proptosis.[20,21]

While imaging can be useful in differentiating between active and quiescent TED,[22] to the authors' knowledge standardized cross-sectional muscle to orbit areas have not been evaluated in predicting NOPD. This study establishes that an enlarged cross-sectional area of each rectus muscle to the orbit, and a smaller fat to orbit ratio, are correlated with NOPD.

Differences in surgical techniques are associated with varying risks of developing NOPD. For medial wall decompression, the endoscopic approach was found to be correlated with lower risk compared to the transorbital approach. In 2011, a Swiss group reviewed 485 articles in the literature and identified 37 case series that studied the unwanted sequelae of NOPD.[6] In contrast, their review highlighted rates of new postoperative diplopia to be 60%, 64%, and 9.5% with the endoscopic medial wall, transantral medial wall, and combined endoscopic and transconjunctival approach for inferior medial wall with strut preservation, respectively.[18,23,24] It may be that there is a spectrum of endoscopic approaches, and the varying incidences of diplopia are highly technique-dependent. We did not sub-stratify endoscopic techniques and grouped all cases of endoscopic medial wall decompression together. In our study, endoscopic procedures were performed at 3 institutions. A periorbital sling was used in 56% of cases, all performed at a single institution, which may also influence the protective effect.

The sling technique used during periorbital fenestration has been described to prevent medial rectus shift after medial wall decompression, whereby a horizontal strip of periosteum is left to prevent the prolapse of the medial rectus into the ethmoid sinus theoretically further decreasing NOPD.[25] The impact of fenestrating the periosteum was studied by Mainville and Jordan, who evaluated 217 orbits of 123 patients who underwent either 1, 2, or 3 wall decompressions. The periorbita was incised in some cases during the medial decompression to allow for the medial rectus and periorbital contents to prolapse into the ethmoid sinuses. The authors identified a 29.7% onset of new postoperative diplopia; varying from 11.8% when the periosteum was kept intact, which increased to 40% when the periorbita was fully opened.[15]

Probability estimation of post-operative diplopia (p*)
$p = e^{logit}/[1 + e^{logit}]$
Where *Logit output of developing diplopia (logit)* = 1.06**a* -1.36**b* -0.60*c* -0.36*d -0.17**e* + 0.27**f* + 0.78 **g* + 1.85**h* -1.07**i* -1.06**j* +0.30 **k* + 0.55**l* + 0.36**m* + 0.05**n* -2.68

Independent Variable	Description	Type
a	Discrete fat to orbit ratio	0: >75% fat 1: 50-75% fat 2: 25-50% fat 3: <25%
b	Age 20-40 years	0: no 1: yes
c	Age 40-60 years	0: no 1: yes
d	Age 60-80 years	0: no 1: yes
e	Female	0: no 1: yes
f	Radioactive iodine history	0: no 1: yes
g	Bilateral surgery	0: no 1: yes
h	Peribulbar steroids	0: no 1: yes
i	Medial endoscopic approach	0: no 1: yes
j	Strut preservation	0: no 1: yes
k	Balanced decompression	0: no 1: yes
l	Floor decompression	0: no 1: yes
m	Systemic steroid use	0: no 1: yes
n	Smoking history	0: no 1: yes

FIG. 2. Modeling the data: multivariable logistic regression analysis. full color online

It has been postulated that new-onset diplopia could be reduced by preserving the inferomedial orbital strut and thereby minimizing orbital shift, and preserving the anterior 10–15 mm of the orbital floor.[6] On multivariable logistic regression analysis, our study identified strut preservation to be an effective measure to reduce the incidence of NOPD.

It has also been suggested that patients who undergo balanced medial and lateral wall decompression are more likely to have symmetric medial and lateral rectus shifting, thereby theoretically reducing the risk of postoperative diplopia.[26] Our study found balanced decompression to harbor an increased risk of developing NOPD. In reviewing the literature, 1 group looked at balanced endoscopic medial and lateral decompression via upper eyelid crease and found a 40% rate of NOPD,[27] whereas a different study combined both transcaruncular or endoscopic medial wall decompressions with lateral decompression and found a 10% rate of NOPD.[28] From our study and literature review, it appears that the wide range of medial wall decompression techniques leads to the greatest variance in diplopia onset post decompression. This study does confirm that surgical indications and clinical case features also play an important role in the risk of NOPD.

Analysis of our cohort revealed that lateral decompression similarly did not increase the risk of NOPD, whereas bilateral surgery did. One study sought to compare balanced orbital decompression (medial and lateral walls) to deep lateral wall decompression. The authors identified rates of NOPD in 33% (3/9 patients) who underwent balanced decompression, compared to only 7% (1/14) of patients who had isolated lateral wall decompression.[16] Several similar studies looked at sole lateral

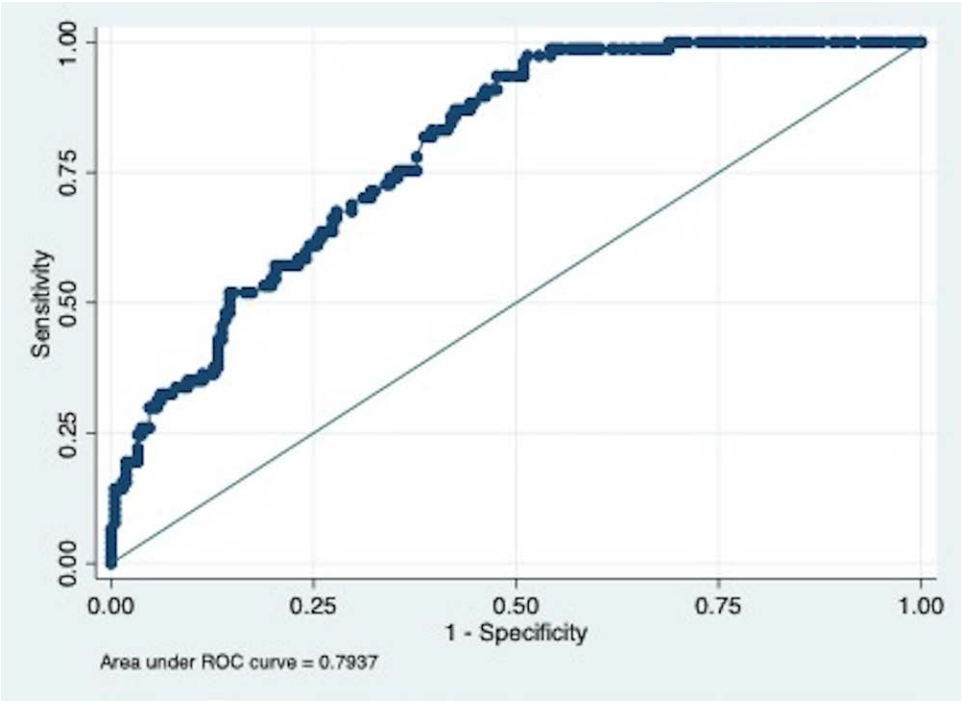

FIG. 3. Multi-variable regression analysis with receiver operating characteristic (ROC) curve. ROC curve for a multivariable logistic regression model predicting probability of developing postoperative diplopia following orbital decompression for thyroid eye disease. full color online

wall decompression via transconjunctival or swinging eyelid approach and found rates of NOPD to be 0%–5.7%.[6] Published rates of NOPD following 3-wall decompression are reported to be 1.8%–12.5%.[29,30] Interestingly, our results also show that 3-wall decompression with preservation of the inferior medial strut does not statistically increase the risk of NOPD.

This is the first study that reports a multivariable logistic regression model to predict NOPD. Our logistic regression model does allow the clinician to estimate the theoretical possibility of diplopia based on this cohort of patients. Application of this formula to broader populations will require validation. Also, as this is a retrospective multicenter study, it does have some shortcomings. The lack of standardized protocols for perioperative steroid treatment, and potential biases, such as the tendency for medical therapy over surgical therapy at each individual center may have played a role in management. Although an effort was made to include surgeons that collectively performed similar procedures, there are likely some minor differences that are not standardized. Patients with worsening preexisting diplopia following surgery are another interesting cohort that was not studied in this article. As a retrospective study, the degree of intermittent diplopia and gaze-induced diplopia was not reliably assessed across the centers and therefore this cohort was not included in this study. We focused solely on primary gaze diplopia. Prior antithyroid therapy information was also not collected in this cohort of patients. All surgeons fenestrated the periosteum during surgery; consequently, fenestration was not included as a variable, which as seen in other studies, may play a role, particularly in medial wall decompression. The type of periosteal fenestration was only studied for the endoscopic medial approach. Finally, it is possible that the ROC curve is over-fit with too many variables. Given the size of our patient population, we were unable to divide the current dataset into a testing and validation cohort. Future directions include validating the model with a new cohort of patients, and corroborating the overall results via prospective, randomized, orbital volumetric studies.

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