

# Predictive factors of visual function recovery after pituitary adenoma resection: a literature review and Meta-analysis

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## Abstract

• **AIM:** To determine the dominant predictive factors of postoperative visual recovery for patients with pituitary adenoma.

• **METHODS:** PubMed, Google Scholar, Web of Science and Cochrane Library were searched for relevant human studies, which investigated the prediction of the postoperative visual recovery of patients with pituitary adenoma, from January 2000 to May 2017. Meta-analyses were performed on the primary outcomes. After the related data were extracted by two independent investigators, pooled weighted mean difference (WMD) and odds ratio (OR) with 95% confidence interval (CI) were estimated using a random-effects or a fixed-effects model.

• **RESULTS:** Nineteen studies were included in the literature review, and nine trials were included in the Meta-analysis, which comprised 530 patients (975 eyes) with pituitary adenoma. For the primary outcomes, there was a significant difference between preoperative and postoperative mean deviation (MD) values of the visual field (WMD -5.85; 95%CI: -8.19 to -3.51;  $P < 0.00001$ ). Predictive

characteristics of four factors were revealed in this Meta-analysis by assigning the patients to sufficient and insufficient groups according to postoperative visual field improvements, including preoperative visual field defect (WMD 10.09; 95%CI: 6.17 to 14.02;  $P < 0.00001$ ), patient age (WMD -12.32; 95%CI: -18.42 to -6.22;  $P < 0.00001$ ), symptom duration (WMD -5.04; 95%CI: -9.71 to -0.37;  $P = 0.03$ ), and preoperative peripapillary retinal nerve fiber layer (pRNFL) thickness (OR 0.1; 95% CI: 0.04 to 0.23;  $P < 0.00001$ ).

• **CONCLUSION:** Preoperative visual field defect, symptom duration, patient age, and preoperative pRNFL thickness are the dominant predictive factors of the postoperative recovery of the visual field for patients with pituitary adenoma.

• **KEYWORDS:** pituitary adenoma; visual function recovery prediction; retinal thickness; visual field defect

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## INTRODUCTION

Pituitary adenomas, especially nonfunctioning pituitary adenomas, have many opportunities to produce visual impairment due to damage to the optic chiasm, including direct compression and disturbances of the blood supply of the optic chiasm<sup>[1-6]</sup>. Visual dysfunction can be associated with visual acuity (VA) deterioration, visual field (VF) defects, color vision deficit, optic disc atrophy and oculomotor abnormalities<sup>[7-8]</sup>. Surgery can improve vision in most patients with pituitary adenoma by excision of the lesions decompressing the anterior visual pathways<sup>[7,9-10]</sup>. Because visual recovery situations vary among patients, preoperative evaluation and predictive prognosis are becoming common issues of concern for both neurosurgeons and patients.

Some studies have focused on the prediction of visual recovery after pituitary adenoma surgery. By using statistical analysis methods, these studies have determined the relationships between all possible factors and visual function before and

after treatment, as well as the best prognostic factors. With our growing understanding of the close relationships among changes in the retina, the deterioration of visual function and damage to the optic chiasm induced by pituitary adenoma, the retina has gradually become the focus of research for the postoperative visual recovery prediction of patients with pituitary adenoma. Besides the characteristics of the patients and tumors, retinal layer measurements, especially retinal nerve fiber layer (RNFL) thickness measured by optical coherence tomography (OCT) devices<sup>[11-13]</sup>, have been used to reveal the relationship between changes in the pituitary gland and visual function loss.

Individual studies have revealed the links between pituitary adenoma and the optic chiasm or the retina, but there has been a lack of summarization of the results from studies of the predictive factors for visual recovery after pituitary adenoma resection. This study fills this gap by reviewing related articles, particularly determining the dominant predictive factors in predicting the postoperative visual outcome of patients with pituitary adenoma.

## MATERIALS AND METHODS

**Literature Search Strategy** The literature review considered studies of the postoperative visual recovery prediction of patients with pituitary adenoma. In the following databases, data source articles from January 2000 to May 2017 were searched: PubMed, Google Scholar, Web of Science and Cochrane Library. A full-text search was conducted using the following terms: “pituitary adenoma” AND “visual recovery” AND “predictive factors” or “prediction”, AND “retinal thickness” OR “optical coherence tomography” OR “OCT”. No restriction was placed on the language of the publication. The reference sections of the relevant reviews and original articles were also scanned for potential trials that may have been missed in the primary searches.

**Inclusion and Exclusion Criteria** To reveal the predictive factors in the postoperative visual recovery for pituitary adenoma, the studies included in the Meta-analysis had to meet the following criteria: 1) non-randomized controlled trials (non-RCT), which studied the relationships between the possible predictive factors and the visual function before and after treatment; 2) at least one of the primary outcomes [VF, VA, best-corrected visual acuity (BCVA), RNFL thickness], or secondary outcomes [macular thickness, ganglion cell complex (GCC) thickness]; 3) enrolled a minimum of 10 eyes. Studies were excluded if they: 1) included patients with diseases other than pituitary adenoma or pituitary tumor that cause chiasmal compression, including craniopharyngioma and suprasellar meningiomas; 2) had no original data (reviews, comments or letters); 3) were not conducted in humans.

**Data Extraction and Quality Assessment** In each of the included studies for literature review, the characteristic

information (type of study, country and year of publication, the number of subjects and studied eyes, age, and gender) and the detailed research strategy information (study apparatus, observation time points, observation factors and conclusive predictive factors) were extracted. For the Meta-analysis, the raw data of the preoperative and postoperative visual function outcomes were carefully collected. Data that could not be obtained were calculated when necessary. All data were extracted from the published studies, and we did not contact the authors for further information. To avoid bias in the data extraction process, all the data and information collection were independently conducted by two individual researchers (Sun M and Chen XJ) following the selection criteria described above. Any discrepancy was resolved by discussion and consensus. The standardized forms of abstraction database were established in Microsoft Excel. We evaluated the quality of the studies included in the Meta-analysis with the Newcastle-Ottawa Scale (NOS)<sup>[14]</sup> for non-RCTs. The range of NOS is from 1 to 9. A score  $\geq 7$  indicates good quality.

**Statistical Analysis** Using VF defects, the Meta-analysis revealed the relationships between visual function recovery and several factors, such as the age of the patient, mean deviation (MD) value of preoperative VF, the duration of symptoms, and preoperative peripapillary retinal nerve fiber layer (pRNFL) thickness. All statistical analyses in the Meta-analysis were performed using Review Manager Software (version 5.3; Cochrane Collaboration, Oxford, United Kingdom). The weighted mean difference (WMD) and odds ratio (OR) with 95% confidence interval (CI) were calculated for the statistical analyses of continuous and dichotomous outcomes. Statistical heterogeneity was tested using Chi-square test and quantified by  $I^2$ . If significant heterogeneity ( $P < 0.1$  and  $I^2 > 50\%$ ) was detected in the Meta-analysis, the random-effects model was used to pool the measurements; otherwise, a fixed-effects model was used. A  $P$ -value less than 0.05 was considered statistically significant.

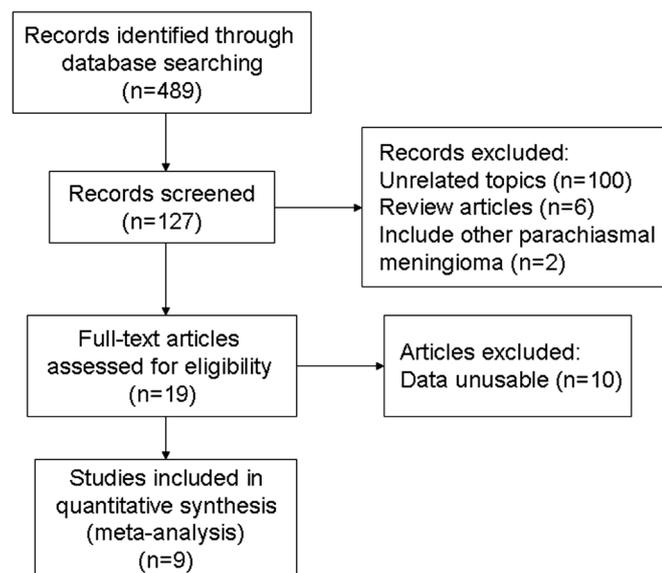
## RESULTS

The literature search yielded 489 references by the search terms. After duplicates were removed, the titles and abstracts of potentially relevant articles were scanned, and 362 studies were excluded. Among the 19 articles that satisfied the inclusion criteria of the literature review, 9 articles were eligible for inclusion in the Meta-analysis. The flowchart in Figure 1 shows the literature search process.

**Summary Characteristics of Included Studies** The characteristics and detailed research strategies of the nineteen studies<sup>[5,7-8,15-30]</sup> are listed in Tables 1 and 2. Eighteen included studies were prospective or retrospective cohort studies, and only one was a prospective case-control study. All the included articles had preoperative and postoperative visual function observations, and the follow-up duration ranged from one week to five

**Table 1 Characteristics of included studies in the review of predictive factors for visual recovery after pituitary adenoma resection**

First author (a)	Type of study	Country	No. of subjects (eyes)		Age (range; a)		Gender (M/F)	
			Patients	Controls	Patients	Controls	Patients	Controls
Gnanalingham <sup>[15]</sup> (2005)	Retrospective cohort	UK	41 (82)		56±2 (30-80)		21/20	
Tokumaru <sup>[16]</sup> (2006)	Retrospective cohort	Japan	27 (54)		51.6±14.0 (21-74)		12/15	
Danesh-Meyer <sup>[17]</sup> (2008)	Prospective cohort	New Zealand	35 (63)		45±16 (18-77)		17/18	
Jacob <sup>[18]</sup> (2009)	Prospective cohort	France	19 (37)	23 (46)	52.26±14.3	41.91±11.7	16/3	2/21
Monteiro <sup>[19]</sup> (2010)	Retrospective cohort	Brazil	30 (60)		44.1±16.0 (23-74)		17/13	
Okamoto <sup>[7]</sup> (2010)	Retrospective cohort	Japan	74 (148)		48.2±13.9 (20-79)		33/41	
Moon <sup>[20]</sup> (2011)	Prospective case-control	Korea	18 (18)	20 (20)	56.75±9.83	53.60±8.43		
Amin <sup>[21]</sup> (2012)	Prospective cohort	Bangladesh	30 (60)		36.2±13.7 (16-70)		16/14	
Barzagli <sup>[8]</sup> (2012)	Retrospective cohort	Italy	73 (139)		52.2±1.25 (16-81)		45/28	
Jahangiri <sup>[22]</sup> (2012)	Retrospective cohort	USA	75		55 (22-82)		46/29	
Ohkubo <sup>[23]</sup> (2012)	Retrospective cohort	Japan	12 (23)		46.3±16.8 (20-77)			
Schmalisch <sup>[5]</sup> (2012)	Retrospective cohort	Germany	98		50.1 (23-86)		57/41	
Lee <sup>[24]</sup> (2013)	Retrospective cohort	Korea	85 (170)					
Garcia <sup>[25]</sup> (2014)	Retrospective cohort	France	34 (68)		53.0±16.0		16/18	
Ho <sup>[26]</sup> (2015)	Retrospective cohort	Taiwan, China	78		47.1±15.4		41/37	
Danesh-Meyer <sup>[27]</sup> (2015)	Retrospective cohort	New Zealand	107 (213)		53.7±15.3 (16-90)		58/49	
Yoneoka <sup>[28]</sup> (2015)	Retrospective cohort	Japan	35 (70)		57.6 (30-77)		22/13	
Yu <sup>[29]</sup> (2015)	Retrospective cohort	China	201 (366)		44.23±1.29 (15-73)		108/93	
Phal <sup>[30]</sup> (2016)	Retrospective cohort	Australia	17 (34)		59.8±12.2 (32-78)		12/5	



**Figure 1 Flow diagram of the literature search in this review.**

years. In these studies, researchers have analyzed different perspectives and have used different equipment, including multifarious ophthalmic devices (VF analyzer, Snellen chart, photo negative response, ophthalmoscope and others), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI) and OCT. The observation factors included various aspects of visual function (VF, VA, photo negative response, color vision), visual pathway indicators (pRNFL thickness, macular GCC volume, area or thickness, the status of optic disk pallor, MRI signal intensity of the optic nerve, DTI tensor parameters

of the optic radiation, activation of the visual cortex on fMRI), and the baseline characteristics of the participant (age, sex, duration of symptoms) and tumor (type, size, and suprasellar tumor extension). The main conclusive predictive factors were preoperative VF defect, duration of symptoms, age of the patient, tumor size and preoperative pRNFL thickness.

Visual results from nine studies in the Meta-analysis are listed in Table 3. There were 530 patients, and 975 eyes were analyzed. The sample sizes ranged from 12 to 201. The mean age of the patients in these studies ranged from 36.2 to 59.8y.

**Postoperative Visual Field Recovery** Preoperative and postoperative VF MD values were available in five trials that included 303 eyes. Five studies showed significant heterogeneity ( $P=0.0006$ ,  $I^2=80\%$ ). A statistically significant difference was found in this outcome (WMD -5.85; 95% CI: -8.19 to -3.51;  $P<0.00001$ ) (Figure 2).

**Preoperative Visual Field Defects and Postoperative Visual Field Recovery** Preoperative VF MD values were available in two trials. These studies showed significant heterogeneity ( $P=0.04$ ,  $I^2=75\%$ ). A statistically significant difference was found in this outcome between the sufficient and insufficient postoperative VF improvement groups (WMD 10.09; 95% CI: 6.17 to 14.02;  $P<0.00001$ ), suggesting that less preoperative VF loss could predict better postoperative VF recovery (Figure 3).

**Age and Postoperative Visual Field Recovery** The preoperative ages of the patients were available in three trials. These studies showed significant heterogeneity ( $P<0.00001$ ,  $I^2=99\%$ ). A significant difference was found in this outcome between the

**Table 2 Detailed research strategies of included studies**

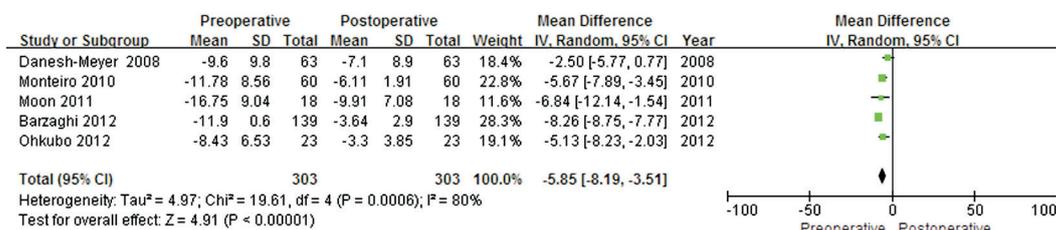
First author (a)	Main apparatus	Observation time points	Observation factors	Predictive factors
Gnanalingham <sup>[15]</sup> (2005)	Humphrey field analyzer II	Preoperatively, postoperative 1wk, 3-6mo, 1, 2 and 5y follow-up	VF	Preoperative VF
Tokumaru <sup>[16]</sup> (2006)	MRI	Preoperatively and postoperatively	Optic nerve signal intensity, degree of optic chiasm compression, VA, disease duration, tumor size	Disease duration
Danesh-Meyer <sup>[17]</sup> (2008)	Stratus OCT, Humphrey field analyzer 2	Within 2mo before surgery and within 6wk after surgery	Thickness of RNFL at 3.4 mm diameter around the disk, BCVA, VF, color vision	pRNFL thickness
Jacob <sup>[18]</sup> (2009)	OCT 3.0, Automated VF analyzer	1mo before treatment, 2wk and 3mo after treatment	VF, RNFL thickness, BCVA	Inferior RNFL thickness
Monteiro <sup>[19]</sup> (2010)	Humphrey field analyzer	Before and after treatment for the tumor	VA, VF, optic disc pallor, tumor size	Degree of optic atrophy, severity of VF defect, tumor size
Okamoto <sup>[7]</sup> (2010)	Humphrey field analyzer	Before and 3mo after surgery	Type and size of tumor, VFQ-25 composite score, BCVA, VF	Preoperative VFQ-25 composite score and VF
Moon <sup>[20]</sup> (2011)	Cirrus spectral-domain OCT, Humphrey field analyzer II, Burian-Allen ERG electrode, Grass PS22 and Grass-Telefactor	Before and 3mo after surgery	pRNFL thickness, GCC area, PhNR/b-wave amplitude ratio, VF	RNFL thickness, GCC area, and PhNR/b-wave amplitude ratio
Amin <sup>[21]</sup> (2012)	Octopus or Humphrey VF analyzer, Snellen chart, ophthalmoscope	Before and 7d after surgery	VA, VF, age and sex of patient, presence or absence of optic atrophy, duration of symptoms, size or volume of tumor, suprasellar extension, method of surgery, extent of tumor resection	Preoperative visual status, duration of symptoms
Barzaghi <sup>[8]</sup> (2012)	Humphrey field analyzer, Snellen chart, ophthalmoscope	Preoperatively, mean postoperative follow-up was 27.0±2.3mo	Tumor size, VF, age, VA	Preoperative visual function, cranio-caudal tumor diameter, age
Jahangiri <sup>[22]</sup> (2012)	VF analyzer	Between 6wk and 6mo after surgery	Tumor size, VF, VA, duration of symptoms, age	Duration of symptoms
Ohkubo <sup>[23]</sup> (2012)	Stratus OCT, RTVue-100	Before and from 1 to 2wk after surgery	Macular GCC volume, VF	Preoperative GCC parameters
Schmalisch <sup>[5]</sup> (2012)	ScanJet 6100C/T, Goldmann kinetic perimetry	Preoperatively 3mo postoperative follow-up	Suprasellar extension of tumor, position of the optic chiasm in relation to the suprasellar adenoma	Suprasellar extension of tumor
Lee <sup>[24]</sup> (2013)	Goldmann perimetry	Before and after trans-sphenoidal pituitary adenectomy	Systemic and visual symptom duration, tumor size, presence of suprasellar tumor extension, histological classification of tumor, VA, and VF	Preoperative VF, preoperative VA
Garcia <sup>[25]</sup> (2014)	Stratus OCT, Kinetic automated perimetry	Preoperatively and mean 19wk postoperative follow-up	pRNFL thickness, VF, BCVA	Nasal peripapillary RNFL thickness
Ho <sup>[26]</sup> (2015)	Goldmann perimetry, Snellen chart	Before and 6mo after surgery	Tumor size, VF, BCVA	Tumor size
Danesh-Meyer <sup>[27]</sup> (2015)	Stratus OCT, Humphrey field analyzer 2	Preoperatively 6-10wk and 9-15mo postoperative follow-up	Thickness of RNFL at 3.4 mm diameter around the disk, macular thickness and volume, BCVA, VF	pRNFL thickness
Yoneoka <sup>[28]</sup> (2015)	RTVue-100, Goldmann kinetic perimetry	2wk before, within 2wk and 3mo or later after surgery	Thickness of RNFL at 3.45 mm diameter around the disk, GCC thickness, BCVA, VF	RNFL thickness and preoperative VF
Yu <sup>[29]</sup> (2015)	MRI, Humphrey field analyzer 750, Snellen chart	Before and 3mo after surgery	BCVA, VF, duration of symptoms, age, and sex, volume of tumor, expression levels of VEGF and Ki-67 in tumor tissue	Age, preoperative VF, volume of tumor, expression levels of VEGF and Ki-67
Phal <sup>[30]</sup> (2016)	Stratus OCT, Trio 3T MRI unit (Siemens)	At least 12mo after surgery	RNFL thickness, FA and MD in the optic radiation, activation of the visual cortex	FA in the optic radiation, activation of the visual cortex

VF: Visual field; MRI: Magnetic resonance imaging; VA: Visual acuity; BCVA: Best-corrected visual acuity; OCT: Optical coherence tomography; RNFL: Retinal nerve fiber layer; pRNFL: Peripapillary retinal nerve fiber layer; VFQ-25: The 25-item National Eye Institute Visual Function Questionnaire; GCC: Ganglion cell complex; PhNR: Photopic negative response; VEGF: Vascular endothelial growth factor; FA: Fractional anisotropy; MD: Mean diffusivity.

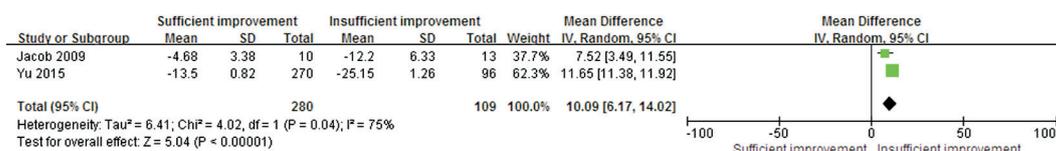
**Table 3 Visual results from nine studies included in the Meta-analysis**

First author (a)	Preoperative pRNFL	State of VF recovery	No. of eyes	VF		NOS score
				Preoperative	Postoperative	
Danesh-Meyer <sup>[17]</sup> (2008)	Normal		43 (with 71% improving to final MD of -3.5 dB or better)	-7.0±8.4	-3.5±5.2	
	Thin		20 (with 28% improving to final MD of -3.5 dB or better)	-15.3±10.3	-13.3±10.6	7
	All		63	-9.6±9.8	-7.1±8.9	
Jacob <sup>[18]</sup> (2009)		Full	10	-4.68±3.38	-0.17±0.13	7
		Incomplete	13	-12.2±6.33	-4.90±4.04	
Monteiro <sup>[19]</sup> (2010)			60	-11.78±8.56	-6.11±1.91	8
Moon <sup>[20]</sup> (2011)			18	-16.75±9.04	-9.91±7.08	8
Barzaghi <sup>[8]</sup> (2012)		Complete	68	-15.6±0.8		
		Partial	65	-8.5±0.6		9
	All		139	-11.9±0.6	-3.64±2.9	
Ohkubo <sup>[23]</sup> (2012)			23	-8.43±6.53	-3.30±3.85	8
Danesh-Meyer <sup>[27]</sup> (2015)	Normal		178	-3.96±5.08	-2.0±3.0	
	Thin		35	-9.22±7.45	-7.1±6.2	9
	All		213	-4.85±5.87		
Yoneoka <sup>[28]</sup> (2015)	Normal	Sufficient	36			
		Insufficient	4			9
	Thin	Sufficient	10			
		Insufficient	20			
		Complete	270	-13.5±0.82		
		Partial	96	-25.15±1.26		8

pRNFL: Peripapillary retinal nerve fiber layer; VF: Visual field; MD: Mean diffusivity; NOS: Newcastle-Ottawa Scale.



**Figure 2 Forest plot of the comparison between the preoperative and postoperative VF values.**



**Figure 3 Forest plot of the preoperative VF defect comparison between the sufficient and insufficient postoperative VF improvement groups.**

sufficient and insufficient postoperative VF improvement groups (WMD -12.32; 95% CI: -18.42 to -6.22;  $P < 0.0001$ ), suggesting that patients with younger ages could achieve better postoperative VF recovery (Figure 4).

**Duration of Symptoms and Postoperative Visual Field Recovery** The durations of symptoms were available in three trials. These studies showed significant heterogeneity ( $P < 0.00001$ ,  $I^2 = 99\%$ ). A significant difference was found in this outcome between the sufficient and insufficient postoperative VF improvement groups (WMD -5.04; 95% CI: -9.71 to -0.37;  $P = 0.03$ ), suggesting that a shorter preoperative

duration of symptoms could predict better postoperative VF recovery (Figure 5).

**Preoperative Peripapillary Retinal Nerve Fiber Layer Thickness and Postoperative Visual Field Recovery** A comparison between preoperative normal and thin pRNFL in the proportion of eyes with sufficient VF recovery was conducted in two studies. These studies showed moderate heterogeneity ( $P = 0.22$ ,  $I^2 = 35\%$ ); the total effect size OR in these studies was 0.1 (95% CI: 0.04 to 0.23), and the Z value was 5.33 ( $P < 0.00001$ ), suggesting that sufficient postoperative VF recovery might be associated with preoperative pRNFL thickness (Figure 6).

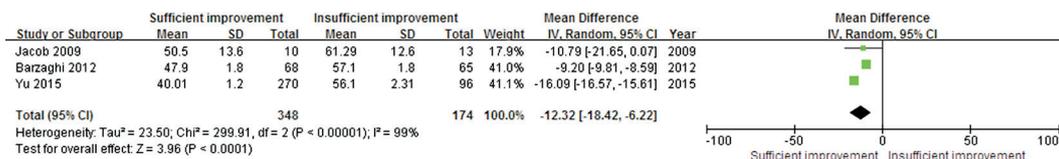


Figure 4 Forest plot of the age comparison between the sufficient and insufficient postoperative VF improvement groups.

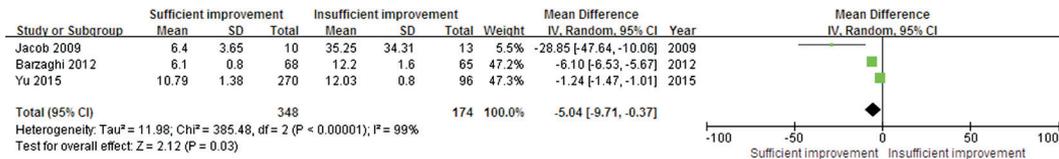


Figure 5 Forest plot of the symptom duration comparison between the sufficient and insufficient postoperative VF improvement groups.



Figure 6 Forest plot of the proportion of eyes with sufficient VF recovery after optic chiasm decompression.

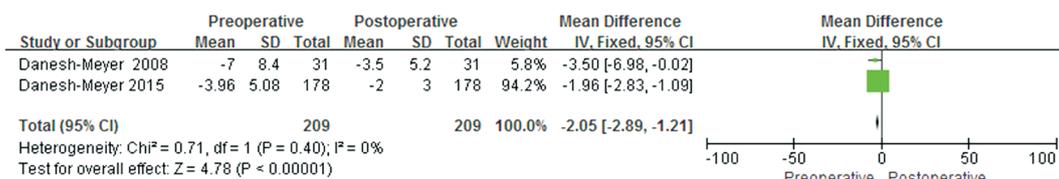


Figure 7 Forest plot of the comparison between the preoperative and postoperative VF for eyes with normal preoperative pRNFL.

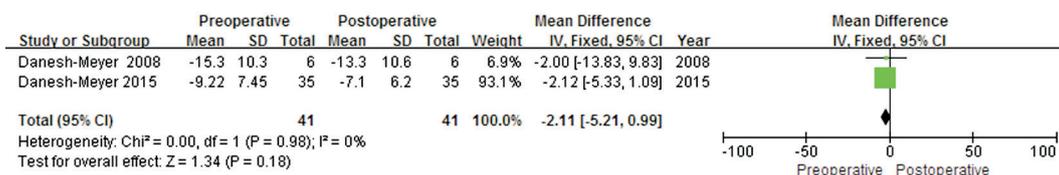


Figure 8 Forest plot of the comparison between the preoperative and postoperative VF for eyes with thin preoperative pRNFL.

A comparison between preoperative and postoperative VF MD values for eyes with normal preoperative pRNFL was conducted in two studies that included 209 eyes. A significant difference was found in this outcome between preoperative and postoperative MD values (WMD -2.05; 95% CI: -2.89 to -1.21;  $P < 0.00001$ ) (Figure 7), suggesting that eyes with normal preoperative pRNFL could achieve good postoperative VF recovery. The heterogeneity test was not significant ( $P = 0.40$ ,  $I^2 = 0$ ).

A comparison between preoperative and postoperative VF MD values for eyes with thin preoperative pRNFL was conducted in two studies that included 41 eyes. No significant difference was found in this outcome between preoperative and postoperative MD values (WMD -2.11; 95% CI: -5.21 to 0.99;  $P = 0.18$ ), with no evidence of heterogeneity ( $P = 0.98$ ,  $I^2 = 0$ ) (Figure 8), suggesting that eyes with thin preoperative pRNFL thickness could not acquire significant postoperative VF improvement.

## DISCUSSION

The studies included in our literature review indicate the dominant predictive factors for the postoperative visual recovery of patients with pituitary adenoma. The Meta-analysis suggests that postoperative VF improvement was significant and factors, such as preoperative VF defects, duration of symptoms, age of the patient, and pRNFL thickness measured by OCT, were closely associated with postoperative recovery of VF.

When the optic chiasm is directly compressed, or its blood supply is affected by a pituitary adenoma, retinal ganglion cell (RGC) axonal injury and visual dysfunction will occur. The three main postulated pathological mechanisms are disruption of conduction along the axon, impairment of axoplasmic flow and demyelination with impaired signal conduction<sup>[9]</sup>. VF defects are the most common and usually the earliest symptom of visual disturbance due to direct compression of the crossing fibers in the optic chiasm by pituitary adenomas. As the disease

develops, the macular fibers can be affected and cause other visual dysfunctions, such as VA damage, color vision loss and optic disc pallor. However, VA impairment, color vision loss, and optic disc pallor are strongly associated with the degree of VF defect<sup>[8,29]</sup>. Therefore, VF defects are emphasized in studies of the correlation between the retina and visual function. The pattern and severity of VF defects depend on the relative position between the optic chiasm and the tumor, as well as the growth direction and size of the tumor<sup>[26,31]</sup>. Larger tumors with greater upward growth increase the pressure on the chiasm, resulting in a more severe degree of visual loss<sup>[19]</sup>. However, our Meta-analysis did not include tumor characteristics because the raw data from the included studies consisted of various forms, including volume, size acquired from coronal or sagittal MRI images, which preventing pooling of the data. Surgical removal is a common therapy for pituitary adenoma and can generally improve the visual function of patients with visual symptoms complaints<sup>[5,10]</sup> (Figure 2). Compared with patients with good preoperative MD values, patients with poor preoperative MD values had worse VF recovery (Figure 3). The duration of visual symptoms refers to the time from the onset of VF loss or diminished VA until the diagnosis of pituitary adenoma. An extended duration of visual symptoms can cause decreased improvement after resection (Figure 5). Excluding subjective delays by patients, visual symptom duration was correlated with the age of the patient. Due to misunderstandings of declining vision among the elderly, older patients are more prone to prolonged visual symptoms than younger patients<sup>[22]</sup>. Compared with a younger patient, an older patient has a lower probability of recovery (Figure 4). In fact, the total number of neurons is smaller in the older retina than that in the younger retina, and neuronal density is lower in most regions of the older retina<sup>[32-33]</sup>, which might be the pathomechanism underlying this phenomenon. However, if the duration of symptoms is less than 6mo, there is no significant difference in visual improvement between older and younger patients<sup>[22]</sup>.

Although these studies reveal strong correlations between various factors and the prediction of visual recovery after pituitary adenoma surgery, the retina as a determining factor of visual function should be considered. The physiological relationship between the retina and optic chiasm ensures that damage to the optic chiasm will affect the retina, especially the RNFL, which comprises RGC axons. Optic nerve fibers originating from the RGCs through the optic disk form the optic nerves, and they also constitute the optic chiasm, with the nasal hemiretinal fibers decussating, while the temporal fibers uncross after entering the cranium<sup>[34]</sup>. Axonal injury-induced RGC death and axon loss will cause RNFL thinning correlated with visual disturbances. The cutoff values differentiating thin RNFL thicknesses from normal thicknesses have usually been

defined as 95% or 97.5% of the normal values derived from age-matched normative databases<sup>[17-18]</sup>. Eyes in the thin nerve group had average preoperative RNFL thicknesses less than the cutoff values.

As a prespecified marker of axonal loss, pretreatment pRNFL thickness measurements by OCT can present the pattern of axonal loss, which might indicate chiasmal compression<sup>[35]</sup>, and can be used to predict visual outcomes after treatment for pituitary adenoma<sup>[36]</sup>. Eyes with visual defects but normal preoperative RNFL thickness showed a significantly greater improvement in postoperative visual function than those with thin preoperative RNFL thickness (Figure 6). Compared with eyes with thin pRNFL, eyes with normal pRNFL had a greater likelihood of achieving approximately normal VFs, indicating an increased propensity for visual recovery (Figures 7 and 8). In addition, if preoperative pRNFL thickness was less than a specific cutoff value for thickness, *e.g.* 85  $\mu\text{m}$ <sup>[17]</sup>, the eyes with thicker pRNFL demonstrated faster restoration of VF defects than those with thinner pRNFL. Long-term follow-up revealed that eyes with normal pRNFL showed the greatest visual recovery within the first 6-10wk after surgery<sup>[17,27]</sup>, and eyes with thin pRNFL showed distinct improvement in the period of 1 to 2y postoperatively<sup>[27]</sup>.

RNFL thinning indicates the loss of ganglion cell axons due to long-term chiasmal lesions. Typically, compression of the optic chiasm will induce an immediate mechanical conduction block along the axon, and persistent pituitary adenoma will affect the axoplasmic flow that provides energy to the RGCs. Then, the anterograde (from the retina to the brain) and retrograde (from the brain to the retina) electrical activity will be impaired, and demyelination and RGC loss, known as retrograde degeneration, will occur<sup>[2,9,37-39]</sup>, resulting in psychophysical visual dysfunctions. Such changes in the axons and RGCs reflect the degree of visual impairment due to a pituitary adenoma, although the retina might manifest normal RNFL thickness. Eyes with visual dysfunction but normal preoperative RNFL thickness had damaged axonal and RGC function accompanied by mostly intact structure, whereas eyes with thin RNFL thickness not only had severe visual defects but also had axonal atrophy and RGC death. When damage to the optic chiasm ended after surgery, most of the dysfunctional RGCs recovered activity in eyes with normal preoperative RNFL. Although there was perhaps prolonged retrograde degeneration, axoplasmic flow was restored, and remyelination occurred. For eyes with thin preoperative RNFL thickness, the severely affected optic nerve and retina might result in prolonged degeneration and delayed restoration of retinal structure<sup>[37]</sup>, which might be explained by the axonal remyelination that creates new concentric lamellar internodes provided by viable adult oligodendrocytes in close proximity<sup>[9,40]</sup>. Other possible explanations include remodeling

by oligodendrocyte progenitors within the anterior visual pathway<sup>9,41</sup> or re-establishment of the vascular supply that was impeded tumor-induced stretching of the chiasmal blood supply<sup>37</sup>.

In conclusion, we presented an overview of studies (published to date) of the predictive factors for visual function recovery after pituitary adenoma resection; the predictive factors generally included preoperative VF, duration of symptoms, age, and pRNFL thickness. There were relationships among these factors, and the visual dysfunction induced by pituitary adenoma was ultimately attributed to retinal damage.

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## Predictive factors of visual recovery for pituitary adenoma

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