• **Meta-Analysis** •

Intraocular pressure fluctuation and the risk of glaucomatous damage deterioration: a Meta-analysis

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Received: 2018-08-19   Accepted: 2018-09-19

Abstract

● **AIM: To systematically review whether the increased fluctuation of intraocular pressure (IOP) is a risk factor for open angle glaucoma (OAG) progression.**
● **METHODS: Scientific studies relevant to IOP fluctuation and glaucoma progression were retrieved from MEDLINE, EMBASE and CENTRAL databases, and were listed as references in this paper. The hazard ratio (HR) was calculated by using fixed or random-effects models according to the heterogeneity of included studies.**
● **RESULTS: Individual data for 2211 eyes of 2637 OAG patients in fourteen prospective studies were included in this Meta-analysis. All studies were longitudinal clinical studies with follow-up period ranging from 3 to 8.5y. The combined HR was 1.23 (95%CI 1.04-1.46, *P*=0.02) for the association between IOP fluctuation and glaucoma onset or progression with the evidence of heterogeneity (*P*<0.1). Subgroup analyses with different types of IOP fluctuation were also evaluated. Results indicated that the summary HR was 0.98 (95%CI 0.78-1.24) in short-term IOP fluctuation group, which showed no statistical significance with heterogeneity, whereas, the combined HR was 1.43 (95%CI 1.13-1.82, *P*=0.003) in long-term IOP fluctuation group without homogeneity. Sensitivity analysis further showed that the pooled HR was 1.10 (95%CI 1.03-1.18, *P*=0.004) for long-term IOP fluctuation and visual function progression with homogeneity among studies (*P*=0.3).**
● **CONCLUSION: Long-term IOP fluctuation can be a risk factor for glaucoma progression based on the presented**

evidence. Thus, controlling the swing of IOP is crucial for glaucoma or glaucoma suspecting patients.
● **KEYWORDS:** intraocular pressure fluctuation; glaucoma; visual field progression

INTRODUCTION

Glaucoma currently represents a leading cause of irreversible vision loss worldwide. Although the progression can be slowed or halted by hypotensive therapy *via* medical, surgical or laser treatments, some patients in clinical practice who fall within the normal range of intraocular pressure (IOP) still suffer from progressive visual function loss[1]. Therefore, besides measuring the IOP, researchers have commenced looking for independent risk factors for glaucoma progression. Potential risk factors as IOP fluctuation, myopia, age, blood pressure and family history have come into researchers' sight[2]. To date, great quantity of studies on such topics have been published, especially in IOP fluctuation, including two of the large well known glaucoma clinical studies: Advanced Glaucoma Intervention Study (AGIS)[3] and Early Manifest Glaucoma Trial (EMGT)[4]. Nevertheless, the coincidence of IOP fluctuation and glaucoma progression had not been concluded within these published studies. For instance, AGIS reported that IOP fluctuation was a risk factor for glaucoma progression[3], while EMGT concluded that IOP fluctuation was not a factor for glaucoma development and progression[4].

Besides, the majority of publications mentioned above which relevant to IOP fluctuation and glaucoma were designed as large longitudinal studies with a long follow-up duration. During such long follow-up period, it is prone to result in censored data from lost to follow-up, death, or other situations. Thus, for these types of data with subsets of inevitable censored data, it has been advocated to be analyzed with Cox proportional hazards model[5] and consider hazard ratio (HR) as combined effect estimate in the Meta-analysis of survival data[6]. Hence, we objected to conduct the Meta-analysis based

on time-to-event data with respect of the conflict relationship between IOP fluctuation and glaucoma onset or progression.

MATERIALS AND METHODS

Search Strategy We systematically searched PubMed, along with EMBASE and CENTRAL electronic database (up to August 2017 respectively) for relevant studies about the association between IOP fluctuation and glaucoma progression. The search strategy for PubMed and EMBASE detailed as: (intraocular pressure$ fluctuation$ OR IOP fluctuation$).af. OR (ocular perfusion pressure$ fluctuation$ OR OPP fluctuation$).af. OR (diurnal IOP OR diurnal intraocular pressure$).af. OR (nocturnal intraocular pressure$ OR nocturnal IOP).af. OR (24 hour intraocular pressure$ OR 24 hour IOP).af. OR (24h intraocular pressure$ OR 24h IOP).af. OR (circadian intraocular pressure$ OR circadian IOP).af. OR (intraocular r pressure curve$ OR IOP curve$). af. OR (intraocular pressure variation$ OR IOP variation).af.. The results of the aforesaid search strategy were incorporated with (glaucoma$ progression$).af.. Similar search terms were used in Cochrane with the pattern "intraocular pressure$ fluctuation$: ti, ab, kw OR IOP fluctuation$: ti, ab, kw in Trials (word variations have been searched)".

All retrieved items were imported into EndNote X7, and those duplicate reports were manually removed. There was no limitation of language. Included papers were shown in the reference, and were further reviewed to identify the potential eligibility.

Inclusion and Exclusion Criteria The studies were included if they met the following criteria: 1) patients were openangle glaucoma (OAG) or suspects; 2) IOP fluctuation as the covariant; 3) visual field or relative glaucomatous structure parameters progression as end point; 4) reported HR estimates with 95% confidence intervals (CIs) from Cox proportional hazards model or allowed to calculate these statistics according to presented data and survival curves[7-8]. IOP fluctuation, a time-dependent variable, was classified into short-term or long-term fluctuation. The short-term fluctuation referred to fluctuation within a time period that was less than or equal to 24h, while the long-term fluctuation was defined as fluctuation within a time period longer than 24h[9]. The long-term fluctuation could be calculated either as the difference between the highest and the lowest IOP values or the standard deviation (SD) of all IOP readings. If the same study population was presented in multiple publications, only the one which the methodology was more homologous to others would be further analyzed to avoid possible bias[10].

Data Extraction and Quality Assessment The following characteristics of each included studies were extracted: first author's last name, publication year, study design, sample type and size, age, follow-up duration, sex distribution, ethnicity

of the study population, type of tonometer and perimetry, definition of IOP fluctuation and glaucoma progression, and adjustment risk factors. Although one of the included reports was published as an abstract in the Association for Research in Vision and Ophthalmology (ARVO) annual meeting[11], its data and the segmental information were completely derived from the AGIS[12].

To compute the combined HR estimates with 95%CIs, data including the natural logarithm HR and standard error (SE) were necessary. Most HR and 95%CIs were reported in the majority of articles that the required data could be easily generated. Only one[11] of the studies provided HR and *P* value, hence the SE value was calculated with formula (logarithm of HR/Z statistic corresponding to *P* value).

There were no validated or established tools for estimating the observational studies quality[13]. Therefore, we examined and compared the included reports with following items: methods for measuring and calculating IOP fluctuation and glaucoma progression, design-specific sources of bias, methods for controlling confounding, statistical methods, and conflict of interest (COI)[14]. All included reports had no COI and were further presented in Tables 1 and 2.

Statistical Analysis Summary effect estimate was calculated with the method of inverse variance. Statistical heterogeneity among studies was examined by the Q test ($P<0.1$ was considered as statistically significant) and measured with I^2 statistic, which was the proportion of between-study variation in total variation[15]. If I^2 was no more than 50%, we used fixed effects model to calculate the pooled HR and 95%CIs. Otherwise the combined effect estimate was calculated with random effects model[16], which not only weighed the study based on sample size, but also based on between-study variation (such as inclusion criteria of cases, age and sex distribution of study populations, and differences in follow-up time) to compensate for the heterogeneity. Sensitivity analysis was conducted to investigate the potential influence on the pooled HR estimate by omitting one or more studies and combining the remainders.

Differences between the subgroups were estimated *via* comparing the combined effect estimates with Chi-square analysis. Potential publication bias was rated by funnel plots. All analyses were run using Review Manager (Version 5.3 Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). A two-tailed *P* value less than 0.05 was considered statistically significant.

RESULTS

Fifteen literatures[4,11,17-29], published from 1998 to 2016, met the inclusion criteria as the flow diagram of screening eligible studies shown (Figure 1). Nevertheless, one study[25] in line with the prespecified rules was excluded on account of the

Table 1 The characteristic of eligible studies

First author, year, country	Mean age (P/S)	Sex (M/F)	Sample size (eyes/subjects)	Mean follow-up period	Criteria for progression	Perimeter (baseline MD)	Definition of IOP fluctuation	Study design
Ishida K, 1998, Japan	56.9	30/80	110/110	51.5mo	VF	HFA30-2 (<15 DB)	24h IOP fluctuation	Observational and longitudinal study
Asrani S, 2000, USA	NA	31/33	105/64	5y	VF and optic disc	NA (various stage)	SD of follow-up IOP	Observational and longitudinal study
Bengtsson B, 2005, Sweden	62	38/52	90/90	8.5y	VF	HFA30-2 (normal)	Diurnal IOP fluctuation	Prospective randomized clinical trail and longitudinal study
Badal F, 2005, USA	35-80	NA	509/401	≥3y	VF	HFA24-2 (<16 DB)	SD of follow-up IOP	Prospective randomized clinical trail
Nakagami T, 2006, Japan	58.2	35/57	92/92	51mo	VF	HFA30-2 (various stage)	The difference of highest and lowest IOP during follow-up	Retrospective observational
Bengtsson B, 2007, Sweden	68.1	86/169	255/255	8y	VF and optic disc	HFA30-2 (<16 DB)	SD of follow-up IOP	Prospective randomized clinical trail
Lee PP, 2007, USA	66	59/70	251/129	5y	VF	HFA (various stage)	SD of follow-up IOP	Observational and longitudinal study
Medeiros FA, 2008, USA	59.5/55.2	53/73	252/126	82.8mo	VF and optic disc	HFA24-2 (normal)	SD of follow-up IOP	Observational and longitudinal study
Sung KR, 2009, Korea	54.2	48/53	101/101	74.8mo	VF	HFA24-2 (MD<20 DB)	SD of follow-up IOP	Observational and longitudinal study
Teng CC, 2010, USA	69.6	94/151	245/245	4.9y	VF	HFA24-2 (4.8±3.8 DB)	SD of follow-up IOP	Observational and longitudinal study
Hoffmann EM, 2014, Germany	NA	NA	NA	NA	HRT	NA	Long-term IOP fluctuation	NA
Lee J, 2014-A, Korea	51.2	26/23	49/49	7.5y	VF	HFA30-2 (MD<16 DB)	SD of follow-up IOP	Observational and longitudinal study
Lee J, 2014-B, Korea	51.7	25/24	49/49	7.7y	VF	HFA30-2 (MD<16 DB)	SD of follow-up IOP	Observational and longitudinal study
Lee J, 2015, Korea	55.83	116/121	237/237	>2y	VF	HFA24-2 (MD<20 DB)	Short-term IOP fluctuation	Observational and longitudinal study
Kim SH, 2016, Korea	53.8/58.1	68/72	140/140	≥5y	VF and optic disc	HFA30-2 (<16 DB)	SD of follow-up IOP	Observational and longitudinal study

P/S: Mean age of progression/stable group; M/F: The number of male/female; VF: Visual field; MD: Mean defect; HFA 30-2/24-2: Humphrey field analyzer central 30-2/24-2 program; SD: Standard deviation; IOP: Intraocular pressure; HRT3: Heidelberg retina tomography-III; NA: Not available.

same study population and statistical method as in the Sung et al[23] study. Therefore, the overview information of final 14 eligible studies were shown as Table 1. All qualified studies referred to 2211 eyes of 2637 OAG patients, except the study with an unavailable study size[26]. These included publications were composed of 2 abstracts from the ARVO annual meeting and 12 full-text articles. Different types of IOP fluctuation reported by all included studies were specified as 4 reports on short-term IOP fluctuation (difference of the nadir and peak IOP within 24h) and 10 studies about the long-term IOP fluctuation (SD of all included IOP readings).

Two reports among the 14 included studies were respectively with two study subgroups, consequently 16 data items (Table 2) were for further Meta-analysis. Among these, eight raw data items were identified that the IOP fluctuation was a statistically significant risk factor for glaucoma progression, and the other eight remainders did not. The pooled HR was 1.23 (95%CI 1.04-1.46, P=0.02), which was computed by random effect model due to statistical heterogeneity (P<0.1).
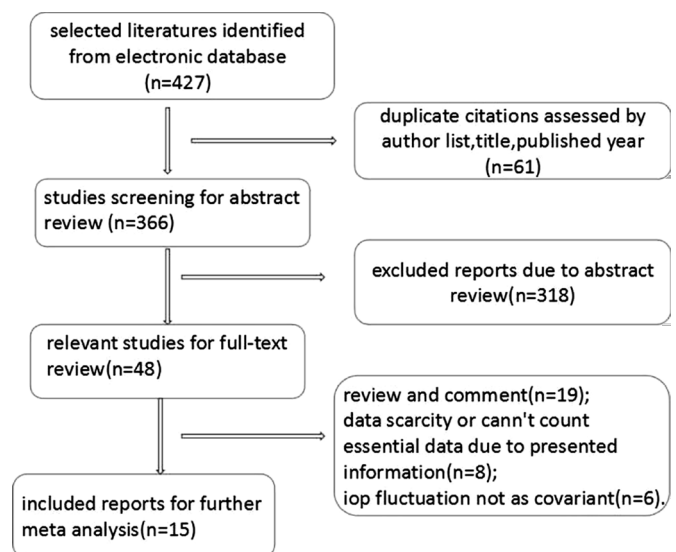

Figure 1 The flow chart showing the screened process of the included studies.

According to different types of IOP fluctuation within eligible publications, stratification analysis was performed between

Table 2 Extracted data items

First author, year, country	Tonometer	Sample type	Mean IOP during follow-up (P/S)	HR	95%CI	P	Adjustment risk factors
Ishida K, 1998, Japan	GAT	NTG	14.4 mm Hg	1.22	1.01-1.4	0.033	Mean IOP, age, sex, HP, DM, VA, MD, CPSD, DH, BP, IOP parameter, recovery rate, pulse rate, follow-up, optic disc,ametropia, treatment
Asrani S, 2000, USA	home tonometry	OAG	16.4 mm Hg	2.89	1.2-6.97	<0.025	Age, office IOP, gender, race, baseline VF damage
Bengtsson B, 2005, Sweden	GAT	OHT	22.7 mm Hg	1.13	0.8-1.6	0.49	Mean IOP
Badal F, 2005, USA	GAT	OAG	15.4/14.5 mm Hg	1.1	NA	0.023	Age, sex, intervention sequence, number of intervention, baseline MD
Nakagami T, 2006, Japan	NA	NTG	13.2 mm Hg	0.724	0.59-0.888	0.002	Age, refraction, mean IOP, DH, baseline VF damage
Bengtsson B, 2007, Sweden	GAT	POAG.NTG. XFG	19.5/16.5 mm Hg	1	0.81-1.24	0.999	Mean IOP, age, baseline MD (≤-4)/iop (>21), both eyes eligible, exfoliation
Lee PP, 2007-1, USA	NA	POAG.NTG. OHT.GS	16.5 mm Hg	4.2	1.3-12.9	0.01	Mean IOP, range of IOP, treatment, sex, age, baseline stage, VF stage
Lee PP, 2007-1, USA	NA	POAG.NTG. OHT.GS	16.4 mm Hg	5.5	3.4-9.1	<0.001	Mean IOP, range of IOP, treatment, sex, age, baseline stage, VF stage
Medeiros FA, 2008, USA	GAT	OHT	25.4 mm Hg	1.08	0.79-1.48	0.62	Mean IOP, age, CCT, vertical C/D ratio and PSD
Sung KR, 2009, Korea	GAT	NTG	13.5/13.6 mm Hg	0.672	0.331-1.362	0.2702	Univariate COX analysis
Teng CC, 2010, USA	Applanation tonometer	POAG.NTG. XFG.other	15.5/16.2 mm Hg	1.17	1.02-1.34	0.02	Mean IOP, baseline IOP/MD, CCT, ametropia, Rim area, PPA, PPA area, PPA/disc ratio
Hoffmann EM, 2014, Germany	NA	NTG	NA	2.03	1.1-3.74	0.02	NA
Lee J, 2014-A, Korea	GAT	NTG	11.8 mm Hg	2.286	0.952-5.492	0.065	Mean IOP, age, sex, ametropia, DM, baseline MD, SBP, DOPP, DH, CCT
Lee J, 2014-B, Korea	GAT	NTG	14.5 mm Hg	0.809	0.198-3.307	0.768	Mean IOP, age, sex, ametropia, DM, DOPP, baseline MD, SBP, DH, CCT
Lee J, 2015, Korea	GAT	NTG	NA	0.87	0.683-1.109	0.26	Age, SE, BMI, baseline MD/PSD, SD of MAP, mean daytime OPP
Kim SH, 2016, Korea	GAT	NTG	14.7 mm Hg	0.311	0.056-1.717	0.18	Mean IOP, age, sex, baseline IOP, CCT, baseline VFI, DH, adjusted SD of IOP

IOP: Intraocular pressure; P/S: Mean IOP of progression/stable group during follow-up; NA: Not available; OHT: Ocular hypertension; NTG: Normal-tension glaucoma; POAG: Primary open angle glaucoma; XFG: Exfoliation glaucoma; GS: Glaucoma suspect; MD: Mean defect; VF: Visual field; CCT: Central corneal thickness; PSD: Pattern standard deviation; VFI: Visual field index; DH: Disc hemorrhage; SE: Spherical equivalent; PPA: Parapapillary atrophy; VA: Visual acuity; GAT: Goldmann applanation tonometer; DM: Diabetes mellitus; HP: Hypertension; MAP: Mean arterial pressure; OPP: Ocular perfusion pressure; BP: Blood pressure; BMI: Body mass index.

short-term IOP fluctuation group and long-term IOP fluctuation group. The difference between two subgroups was statistically significant (P=0.03) and the results showed that the combined HR was 0.98 (95%CI 0.78-1.24, P=0.89) and 1.43 (95%CI 1.13-1.82, P=0.003) respectively for short-term IOP fluctuation group and long-term IOP fluctuation group. However, both pooled HR estimates were with heterogeneity.

Sensitivity analysis showed that the heterogeneity among the group with regard to long-term IOP fluctuation was mainly contributed by the following three studies (Figure 2). These studies were roughly homogeneous with others, except one study was designed as a cohort study[21], another study collected IOP readings by patients using home tonometry measurements[18], and the other study considered the change of Heidelberg Retina Tomography (HRT) as a glaucoma

progression criterion[26]. When omitting these studies, the combined HR was 1.10 (95%CI 1.03-1.18, P=0.004) for long-term IOP fluctuation and glaucoma progression. Furthermore, there was no evidence of heterogeneity (P=0.3, I^2=16%).

DISCUSSION

In this study, we conclude that IOP fluctuation is a risk factor for glaucoma progression. The combined HR was 1.10 (95%CI 1.03-1.18) for long-term IOP fluctuation and glaucoma progression. This also indicates that the risk of glaucoma progression increased by 10% for every 1 mm Hg of long-term IOP fluctuation.

What are the mechanisms of IOP fluctuation act on glaucoma progression? One paper indicated that lamina cribrosa (LC) was the initial site of glaucomatous axons damage[30]. LC is composed of capillaries, astrocytes, fibrocytes and extracellular
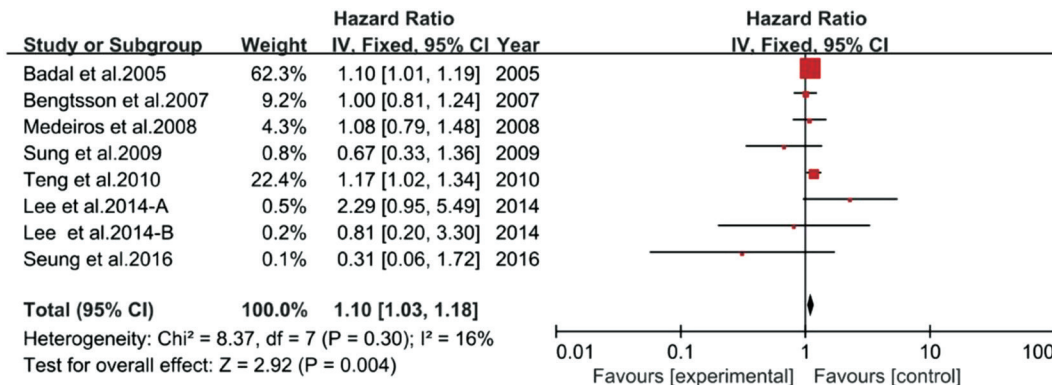
Figure 2 Forest plot shows the result of sensitivity analysis for the subgroup of long-term IOP fluctuation and glaucoma progression.

matrix (ECM), which principally contains various collagens, elastins, and proteoglycans. The LC is endowed biomechanical properties with ECM and has been as an IOP-related stress load-bearing tissue[31]. IOP fluctuation relevant to mechanical stress within the sieve pores could be magnified 122 times by the three dimensional geometry detailed as the overlapped lamellar connective tissues in the scleral canal of spherical ocular shell[32]. A long-term oscillation of mechanical stress can enhance fatiguing effects on collagens and elastins. Once the shear, tensile and compressive stress is beyond loading-limits of fibroelastic tissues, it can cause hypercompliance and permanent deformation to tissues[31]. Meanwhile, the applied stress may activate gliocytes to trigger relevant downstream signaling pathways and result in structural modification of the LC. Proliferative ECM not only makes LC stiffer, but also decreases the efficiency of nutrients delivery from capillaries in LC[33]. Although it's difficult to explore the exact way of how IOP fluctuation damage on glaucoma from the IOP effect *in vivo*, according to the established proof above, we can conclude that IOP fluctuation may related to stress effect on LC and its capillaries to further cause injury of retinal ganglion cells (RGCs). In this Meta-analysis, all included literatures were longitudinal studies with the longest mean follow-up period up to 8.5y. When progressed cases occurred during the follow-up time, the intensified treatment regimen was required for lowering the IOP of patients. Once changing the therapeutic schedule, it must lead to alteration of IOP fluctuation outcome. One study in our analysis, which data were derived from the AGIS, calculated IOP fluctuation including the IOP dataset after changing the therapeutic schedule[11]. This may result in a consequent increase of IOP fluctuation and can lead to a non-naturally positive association between IOP fluctuation and glaucoma progression in the AGIS. When the report of AGIS was removed from our analysis, the combined result 1.28 (95%CI 1.04-1.59, *P*=0.02) was still statistically significant with a slight increase of heterogeneity compared to our previous pooled result (*P*<0.1). However, the reason of deleting one different calculation of IOP fluctuation from

included studies increased the heterogeneity remains unclear. The overall HR was statistically significant with heterogeneity among all observational studies in this Meta-analysis. The present heterogeneity can be interpreted as following aspects. Firstly, the Meta-analysis of observational studies usually is confronted with challenges due to different study designs. Excluding sole cohort study from included studies make heterogeneity (I^2 statistic) decline from 81% to 58%. Secondly, various adjusted confounders included in the Cox proportional hazard model are different among the eligible reports. This can effect on the partial regression coefficient of covariant in the Cox model. Nevertheless, most eligible studies adjusted the important variables as mean IOP, age, gender and baseline mean defect (MD). In fact, some limitations may exist in this paper. The possible publication bias was indicated by funnel plot. Although half of the included studies considered IOP fluctuation as a risk factor, we haven't retrieved those unpublished results. There may subsist possible selection biases among the included studies which had heterogeneous criterion of inclusion and exclusion for each study.

In conclusion, long-term IOP fluctuation is a risk factor for glaucoma progression. When dealing with cases of IOP in clinical practice, both the level of IOP and the smooth IOP fluctuation should be taken into account for slowing down the deterioration of glaucoma. Indeed, the consequence of IOP fluctuation need to be further studied within glaucoma and normal populations. For instance, the threshold of IOP fluctuation that require for medical intervention. Our current findings showed that long-term IOP fluctuation is related to glaucoma deterioration. Thus, it should also be followed in clinic to protect the vision functions of glaucoma patients.

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