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Glaucoma and Ten-Year Mortality: The Liwan Eye Study

Running tilt: Glaucoma and mortality

Research question: The association between glaucoma and 10-year mortality in an adult population in China

Study design: Population-based cohort study

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Tables: 4 **Figure:** 0

Abstract

Objectives: To investigate the association between glaucoma and 10-year mortality in an adult population in China.

Design: Population-based cohort study.

Setting: The Guangzhou Liwan Eye Study.

Participants: A total of 1405 participants aged 50 years and above at baseline examination were invited to attend the 5- and 10-year follow-up examinations.

Primary and secondary outcome measures: The International Society of Geographic and Epidemiologic Ophthalmology criteria was used to define glaucoma. Presenting visual impairment (PVI) was defined as a presenting visual acuity of 20/40 or worse in the better-seeing eye. The 10-year mortality rates were compared using the log-rank test and Cox proportional hazards regression models.

Results: A total of 1372(97.7%) participants with available gonioscopic data were included in the present analysis. Of them, 136(9.9%), 33(2.4%) and 21(1.5%) participants had primary angle closure suspect (PACS), primary angle closure (PAC) and primary angle closure glaucoma (PACG) and 29(2.1%) participants had primary open angle glaucoma (POAG). After 10 years, 306 (22.3%) participants had died. The 10-year mortality were significantly associated with PACG(HR,2.15,95%CI:1.14-4.04) but not associated with PAC, PACS and POAG when age and gender was adjusted for. This association was no longer statistically significant when more co-variables, such as income, educational attainment, BMI, PVI, history of diabetes and hypertension, were adjusted for. Larger vertical cup-to-disc ratio (VCDR>0.30) was only significant risk factor in multivariate analysis (HR,1.60;95%CI,1.11-2.33).

Conclusions: PACG was significantly associated with higher long-term mortality but this association was likely confounded by other systemic risk factors. VCDR>0.3 was the only independent predictor, implying that VCDR might be a marker of ageing and frailty.

Patient and Public Involvement Statement： There were no patients and public involved in the design and process of this study.

Key words: Glaucoma; Mortality; China; Cox proportional hazards regression model

Strengths and limitations of this study

1.The present study was a population-based cohort study with standardized study protocol

2. The use of the International Society of Geographic and Epidemiologic Ophthalmology criteria to define glaucoma

3. Study limitations include the following: 1) the small number of patients with glaucoma;2) several important confounding factors, such as smoking were not available.

Introduction

Glaucoma, one of the leading causes of irreversible visual impairment (VI) and blindness, affects approximately 64.3 million people worldwide.[1] It has been estimated that the number of people diagnosed with glaucoma in China was 13.1 million in 2015, with more than half of those diagnosed with primary angle closure glaucoma.[2] As the population continues to age, the number of people with glaucoma in China is expected to reach 15.2 million by 2050.[2]

In addition to its impact on vision and quality of life, some studies have indicated that patients with glaucoma have higher rates of mortality,[3-6] while others have found no association,[7-18] leading to controversies regarding the risk of premature mortality of patients with glaucoma. Similarly, inconsistent evidence has been observed for the association between level of intraocular pressure (IOP), a well-established functional risk factor for glaucoma, and survival.[14, 17, 18] The relationship between mortality and vertical cup-to-disc ratio (VCDR), a robust structural indicator of glaucomatous loss of the neuroretinal rim, has been exclusively investigated in the Andhra Pradesh Eye Disease Study (APEDS), implying that nerve fiber loss may be a marker of ageing and frailty.[7] Of note, previous studies, mainly in white and black populations, investigated the relationship between primary open angle glaucoma (POAG), elevated IOP and long-term survival.[8-10, 12, 14, 15, 18, 19] Few studies have been conducted in Asian populations.[3, 4, 7, 11, 13, 16] Furthermore, dominant subtypes, clinical presentations and the underlying pathogenesis of glaucoma vary in Asian populations compared to white and black populations.[20, 21] A better understanding of the relationship between different subtypes of glaucoma (POAG and primary angle closure disease (PACD)), level of IOP, VCDR and risk of mortality may provide insights into the potential mechanisms and clinical management of glaucoma.

Therefore, the aim of this study was to explore the relationship between different types of glaucoma, level of IOP, VCDR and 10-year mortality in an adult population in southern urban China.

Methods

Study Population

A detailed description of the methodology utilized in the Liwan Eye Study has been described previously.[22] Briefly, the Liwan Eye Study was a population-based cohort study initiated in 2003 with a five-year follow-up from 2008 to 2009 and a ten-year follow-up in 2013 following an identical protocol. At baseline, 75.4% (1405 of 1864) of eligible participants underwent a comprehensive eye examination and a questionnaire regarding income, education, and medical history. All participants in the baseline study were invited to take part in the five- and ten-year follow-up examinations. A total of 924 participants (75.0% of survivors, 79.1% of eligible participants) returned for the five-year examination and 791 participants (73.8% of survivors, 86.2% of eligible participants) for ten-year examination.

Ethical approval for the study was obtained from the Zhongshan University Ethics Review Board, and the Research Governance Committee of Moorfields Eye Hospital, London. The study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from all participants.

Study procedure

All participants had their presenting visual acuity (PVA) with habitual refractive

correction tested using an Early Treatment Diabetic Retinopathy Study (ETDRS) vision chart. Best-corrected visual acuity (BCVA) was measured for those with PVA ≤ 20/40 in either eye. Presenting visual impairment (PVI) was defined as PVA less than 20/40 in the better-seeing eye. The IOP was measured before mydriasis by a handheld tonometer (Tonopen; Mentor, Norwell, Massachusetts, USA) with three consecutive measurements achieving standard error <5%. Central cornea thickness (CCT) was evaluated using an ultrasound pachymetry (Echoscan US1800; Nidek,Corp). Height and weight were measured without shoes, using a standard calibrated scale. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in centimeters and was divided into three group: underweight (BMI <18.5 kg/m^2), normal to overweight (18.5 to30 kg/m^2), or obesity (BMI ≥ 30.0 kg/m^2). Diabetes mellitus (DM) and hypertension were based on self-reported history of a diagnosis and/or previous medication use.

Slit-lamp examination (TopconSL-8Z, Tokyo, Japan) with a 78-diopter lens was used to identify abnormalities of the anterior segment and posterior segment by an experienced ophthalmologist (MH). Detailed information of the gonioscopic examination in the Liwan Eye Study has been described previously.[22] Briefly, all participants underwent slit lamp based static and dynamic gonioscopy with a Goldmann-type, one-mirror lens (Haag Streit, Bern, Switzerland) at 25x magnification by the same experienced specialist-trained ophthalmologist (MH). Narrow angle and open angle were stratified by status of the iris insertion which was recorded using five categories by the Shaffer system. [23]According to the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) classification, primary angle closure suspect (PACS) was defined as simply an angle in which ≥270°of the pigmented trabecular meshwork cannot be seen without evidence of

trabecular obstruction and glaucomatous damage. Primary angle closure (PAC) was defined as eyes with PACS and features of peripheral anterior synechiae, elevated IOP, iris wholing, or excessive pigment deposition on the trabecular surface, but no evidence of glaucomatous damage. Primary angle closure glaucoma (PACG) was defined as eyes with PAC and evidence of glaucomatous damage. Participants with PACS, PAC or PACG were grouped as PACD.

The optic disc was assessed using a 78-D lens at 16x magnification. The VCDR was used as the key indicator of structural glaucomatous change. Visual field (VF) assessment was performed in those with a VCDR of ≥0.7 in either eye, VCDR asymmetry ≥0.2 or IOP of ≥21 mm Hg on a subsequent day. The definition of glaucoma was based on three levels of evidence using ISGEO criteria, and the division of POAG and PACG was based on the gonioscopic results of narrow angle or open angle. If glaucoma status or VCDR were available for both eyes, the eye with the more severe status or larger VCDR value was used in the analysis.

Detailed data from the Chinese Centre for Disease Control and Prevention (CDC) were used to confirm the mortality of participants during the 10-year follow-up period. After providing the CDC with a list of names, age, year of birth, gender and last known address for the participants that were suspected of having passed away, researchers at the CDC provided a corresponding list of “matched” deaths that included a list of time of death and causes of death for individuals who matched. The CDC recorded causes of death documented on death certificates using the International Classification of Diseases, Ninth Revision.

Statistical analysis

All statistical analyses were performed using Stata (ver. 10.0; Stata Corp, College Station, TX). The student's t-test was used to compare continuous variables, while Pearson chi squire or Fisher's exact test were used for the comparison of categorical data. Survival times were calculated for each participant from the date of baseline examinations through to the date of death or April 30, 2014. Univariate and multivariate Cox proportional hazard regression models were used to test the associations between incident mortality and baseline PACS, PAC, PACG, POAG, IOP and VCDR after adjusting for baseline characteristics of age, gender, education level, family income, history of diabetes and hypertension and PVI. Analysis of IOP and VCDR were based on both continuous level and categorical group. IOP was divided into three categorical groups: 10-21mmHg (reference group), <10mmHg and >21 mmHg. The lowest quartile of VCDR (≤0.3), the third quartile of VCDR in this population (≤0.5) and VCDR of < 0.7 (the common criteria for glaucoma diagnosis) were used as the reference group to assess associations of different VCDR cut-offs with long-term survival. Hazard ratios (HR) and 95% CI were given. A proportional hazard test was used to check the assumption of cox proportional hazards model, and the log-rank test was used to compare different groups with respect to their survival distributions. A p value of < 0.05 was defined to indicate statistical significance.

Results

Of the 1405 participants at baseline, 33 did not have gonioscopic data and were therefore excluded, leaving 1372 available for analysis. Among the 1372 participants, the prevalence of PACS, PAC, PACG, and POAG was 9.9% (136 participants), 2.4% (33 participants), 1.5% (21 participants), and 2.1% (29

participants), respectively. Compared to the 1153 normal participants, those with PACD were more likely to be older (P<0.001), female (P=0.001), underweight (P<0.001), of a lower level of family income (P=0.005) and higher proportion of PVI (P<0.001). There were no statistically significant differences between groups in terms of level of education, hypertension, diabetes, CCT and IOP. Compared to the 1,153 normal participants, those with POAG tended to be older (P=0.003), male (P=0.003) and had a higher proportion of PVI (P=0.001) (Table 1).

By the end of April 2014 (median follow-up length: 9.38 years; range: 0.15-10.2), a total of 306 (22.8%) of the 1,372 participants passed away during the 10-year follow-up. Those who passed away tended to be older (P<0.001), male (P<0.001), had a lower level of educational attainment (P=0.001), lower family income (P<0.001), higher proportion of PVI (P<0.001), larger VCDR (P<0.001) and be underweight (P=0.009). The medical history of hypertension and diabetes, CCT and mean IOP value were similar between the two groups (Table 2).

Among the 1153 participants without PACD or POAG, 235 (20.4%, 95%CI=18.1, 22.8%) passed away during the 10-year follow up period. The 10-year mortality rate was significantly lower than those with PACS (31.6%, 95%CI= 23.9, 40.1%), PAC (30.3%, 95%CI= 15.6, 48.7%), PACG (47.6%, 95%CI=25.7, 70.2%), and POAG (27.6%, 95%CI= 12.7, 47.2%). The age and gender adjusted cox proportional hazards model showed that the presence of PACG (HR=2.15, 95% CI=1.14, 4.04), PACD (HR=1.46, 95% CI=1.10, 1.95) and a VCDR of more than 0.3 (HR=1.53, 95% CI=1.16, 2.01) were significantly associated with a higher risk of mortality. No association was

found between mortality and PACS, PAC, POAG and level of IOP. After adjusting for age, gender, education, income, history of diabetes and hypertension, BMI and PVI, the significant association between VCDR of more than 0.3 and poorer survival rate was still observed (HR=1.60, 95% CI=1.11, 2.33) (Table 3 and Table 4). We further analysed the associations of VCDR>0.5 and VCDR≥0.7 with 10 year mortality, and the results showed that both VCDR>0.5 (HR=1.37, 95% CI=1.06, 1.78) and VCDR≥0.7 (HR=1.62, 95% CI=1.18, 2.20) were strongly associated with mortality in the univariate analysis, whereas these associations disappeared after adjusting for confounders (all P>0.05, Supplement Table 1).

Discussion

In this population-based cohort study, we found a higher (ranging from 7.2% to 27.2%) crude mortality rate among patients with POAG or any form of PACD. However, this difference was not replicated after multivariate confounders were adjusted for. Level of IOP was not significantly associated with an increased risk of 10-year mortality in the multivariate model, while VCDR of more than 0.3 was an independent predictor of long-term poor survival.

Controversy still exists around the association between POAG and increased risk of mortality.[3-10, 12, 14-16, 18, 19] Almost 50 years ago, Egge et al found a decreased 30-year survival rate for patients with glaucoma in Norway. This finding was more pronounced among men using acetazolamide.[6] Results of the National Health Interview Survey (NHIS) 1986-1994 also supported the finding that glaucoma was related to an increased risk of all-cause and cardiovascular disease mortality among adults residing in the United States.[5]

However, the glaucoma-mortality association in the NHIS is likely to have been subjected to recall bias (self-reported definition of glaucoma), misclassification error and underestimation of glaucoma cases. Furthermore, the diagnostic methods, definition and treatments of glaucoma have changed over the past five decades, thus making its findings less generalizable to today's glaucoma patients. More recent studies were in favor of the finding that POAG was not significantly associated with long-term survival.[3, 4,7-10, 12, 14-16, 18] The non-significant relationship in these studies are in agreeance with our results. Differences in ethnicity, age distribution, study design, length of follow-up, definition of glaucoma, and confounding variables adjusted in the multivariate model may explain inconsistent results between studies. Alternatively, the small number of patients with POAG in the current study (n=29) may also explain the lack of association between POAG and 10-year mortality. However, a recent meta-analysis of observational studies[17] also supported a non-significant relationship between POAG and risk of mortality.

Few studies have explored the relationship between different types of PACD and mortality. The present study resulted in similar findings to those who previously investigated that the presence of PACD was not an independent risk factor for all-cause mortality.[7, 11, 13, 16] Thus far, only 5-year data from the Beijing Eye Study has reported that the presence of PACG was related to an increased risk of mortality using multivariate analysis.[3, 4] Interestingly, the 10-year data from the Beijing Eye Study found that mortality was not significantly associated with PACG.[16] Neither the Tanjong Pagar Study[11] or the Singapore Malay Eye Study (SiMES)[13] found statistically reduced survival among those with glaucoma. In the current study, we found that PACG was significantly associated with 10-year mortality in the age and gender adjusted model, but this significant association disappeared in the multivariate model. The

possible reason might be that PACG-mortality association was confounded by other systemic risk factors or relatively small study sample size.

The results of this study found a non-significant association between the level of IOP and 10-year mortality. Previous reports on the relationship between all-cause mortality and elevated IOP have been inconsistent.[7, 14, 18, 19] The excess all-cause mortality associated with ocular hypertension was found in the Barbados Eye Study and in the Framingham Study,[18] while in the APEDS[7] and in a Sweden study,[14] no statistically significant association was found between elevated IOP and mortality risk. The APEDS was the only study to explore the association between VCDR and all-cause mortality. Consistent with the APEDS's finding that the increasing VCDR was a predictor of 10-year mortality,[7] we also reported a significantly increased risk of mortality among participants with VCDR of more than 0.3. Considering that previous studies indicated that global retinal nerve fiber layer decreased significantly with ageing and larger VCDR,[24, 25] one can speculate that the potential mechanism underlying the VCDR-mortality association may be caused by retinal nerve fiber layer thinning, a marker of ageing and frailty. Furthermore, the close relationship between neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease) and glaucoma, and the strong link between retinal nerve fiber layer thinning and brain pathology, again verified our speculation.[26-29] Further studies with a larger study sample are needed to investigate the association between VCDR, retinal nerve fiber layer thickness and mortality. The non-significant association of long-term survival with VCDR$\geq$0.7, a common cut-off for glaucoma diagnosis, might be partly due to the small sample size in our study. Alternatively, we might speculate that only VCDR less than 0.3 (i.e., sufficient retinal nerve fibre layer) might be the threshold for better survival.

Even though the mechanisms underlying glaucoma/ocular hypertension-mortality association is still unclear, it had been speculated that increased risk of mortality among patients with glaucoma or ocular hypertension might be caused by IOP-lowering treatment. Egge found the glaucoma-mortality association was more pronounced among men using acetazolamide.[6] The excess mortality linked to timolol maleate treatment for POAG found in the Barbados Eye Study[18] was also parallel to the hypothesis of this study. In the BMES, a dose-dependent pattern was observed in the association between duration of timolol maleate use and the increased risk of cardiovascular disease mortality. In addition, previous studies verified the adverse effects of IOP-lowering treatments, including congestive heart failure, raised blood pressure and adverse respiratory effects.[30, 31] However, the dose-dependent pattern observed in the BMES might be due to detection bias. Approximately 50-90% of glaucoma patients remain undiagnosed.[7, 32] Participants in poorer health are more likely to access health care services and therefore have their glaucoma diagnosed and treated. The suggestion that detection bias is a cause of variable findings was further verified by the similar mortality rates between treated and untreated glaucoma patients in multicenter randomized glaucoma treatment trials (Early Manifest Glaucoma Trial and Ocular Hypertension Treatment Study) and the observational Rotterdam study (Rotterdam Study).[33-35] Even these two studies concluded that the use of glaucoma medications was associated with a reduced risk of mortality.[36, 37] Future investigations should assess this association further.

The strengths of the present study included the population-based study design, high participation rate, long-term follow-up, and a standardized definition of glaucoma. Of note, the present study was limited by the following points. Firstly, the small number of patients with glaucoma may explain the

non-significant association between different types of glaucoma and mortality. Second, several important confounding factors, such as smoking were not available in the present study. Nevertheless, the additional adjustment for these important confounding factors may further attenuate the magnitude of statistical significance and again verify the robustness of our results. Third, the lack of data on the causes of death prevented the possibility of exploring the association between glaucoma and specific-cause mortality. Previous studies have reported a significant association between glaucoma and cardiovascular disease mortality.[5, 38] Fourthly, the fact that only participants with suspect glaucoma (VCDR of ≥0.7 in either eye, VCDR asymmetry ≥0.2 or IOP of ≥21 mm Hg) underwent VF assessment may underestimate the prevalence of glaucoma because participants with early changes of VCDR due to glaucoma maybe missed. However, each participant underwent IOP measurements and the collection of information on previous history of glaucoma may lower this underestimation. Finally, we did not collect information on utilization of IOP-lowering treatment. Further studies are required to investigate the relationship between IOP-lowering treatment and long-term survival.

In conclusion, our findings suggest there are a higher level of crude mortality among patients with POAG, PACS or PAC. However, this difference was unable to be replicated after multivariate confounders were adjusted for. PACG was significantly associated with 10-year mortality in the age and gender adjusted model, but this significant association disappeared in the multivariate model. The level of IOP was not significantly associated with increased risk of 10-year mortality, while VCDR of more than 0.3 was an independent predictor of long-term survival. Further studies are needed to confirm these findings and to explore the association of different subtypes and treatments of glaucoma with long-term survival.

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Table 1 Baseline Characteristics of participants with POAG, PACG, PAC and PACS.

Basic characteristics	Normal, N (%)	PACD				POAG, N (%)
		PACS, N	PAC, N (%)	PACG, N	Total, N	
Total number (%)	1153(100)	136 (100)	33 (100)	21 (100)	190 (100)	29 (100)
Age (%)						
50-59	440 (38.2)	17 (12.5)	5 (15.2)	0 (0)	22 (11.6)	4 (13.8)
60-69	328 (28.5)	46 (33.8)	12 (36.4)	5 (23.8)	63 (33.2)	7 (24.1)
+70	385 (33.4)	73 (53.7)	16 (48.5)	16 (76.2)	105 (55.3)	18 (62.1)
Female (%)	639 (55.4)	95 (69.9)	26 (78.8)	13 (61.9)	134 (70.5)	8 (27.6)
No more than middle school	809 (79.3)	93 (79.5)	19 (63.3)	12 (70.6)	124 (75.6)	22 (78.6)
Income less than 1000RMB	585 (72.7)	78 (82.1)	22 (88.0)	12 (92.3)	112 (84.2)	19 (70.4)
BMI (kg/m^2)						
Normal (18.5-30.0)	716 (91.6)	79 (85.0)	16 (72.7)	11 (84.6)	106 (82.8)	23 (88.5)
Under weight (<18.5)	39 (4.99)	14 (15.1)	3 (13.6)	1 (7.69)	18 (14.1)	3 (11.5)
Over weight (≥30.0)	27 (3.45)	0 (0)	3 (13.6)	1 (7.69)	4 (3.13)	0 (0)
Hypertension (%)	416 (40.1)	61 (45.9)	15 (45.5)	10 (50.0)	86 (46.2)	16 (57.1)
Diabetes (%)	105 (10.1)	16 (12.0)	3 (9.09)	4 (20.0)	23 (12.4)	3 (10.7)

PVI (%)	228 (19.8)	45 (33.3)	12 (36.4)	10 (47.6)	67 (35.5)	13 (44.8)
CCT(μm)	541.7±33.2	535.5±33.4	542.9±29.8	550.4±26.9	538.4±32.5	542.5±35.2
IOP (mmHg, SD)	15.2±3.04	15.1±2.88	14.8±4.25	19.4±5.36	15.5±3.71	15.8±2.87

Abbreviations: PACD=Primary angle closure disease, POAC=Primary open angle glaucoma, PACG= Primary angle closure glaucoma, PAC= Primary angle closure, PACS= Primary angle closure suspect, BMI=Body mass index, PVI=Presenting visual impairment, CCT=central cornea thickness, IOP=Intraocular pressure

Table 2 Distribution of Basic Characters Associated with Mortality at Baseline Examination.

Basic Factors	Died, N (%)	Alive, N (%)	P-value
Total number (%)	306 (100)	1066 (100)	
Age (%)			<0.001
50-59	23 (7.52)	443 (41.6)	
60-69	66 (21.6)	332 (31.1)	
+70	217 (70.9)	291 (27.3)	
Female (%)	147 (48.0)	634 (59.5)	<0.001
No more than middle school	155 (67.7)	800 (81.4)	<0.001
Income less than 1000RMB	173 (83.2)	543 (71.7)	0.001
BMI (kg/m^2)			0.009
Normal (18.5-30.0)	169 (85.8)	676 (91.5)	
Under weight (<18.5)	22 (11.2)	38 (5.14)	
Over weight (≥30.0)	6 (3.05)	25 (3.38)	
Hypertension (%)	111 (44.4)	407 (40.6)	0.277
Diabetes (%)	33 (13.2)	98 (9.79)	0.120
PVI (%)	120 (39.5)	188 (17.6)	<0.001
VCDR(mean±SD)	0.49±0.18	0.44±0.17	<0.001
CCT(μm)	540.3±35.3	541.5±32.5	0.582
IOP (mmHg, SD)(mean±SD)	15.1±3.32	15.3±3.08	0.495

Abbreviations: PACD=Primary angle closure disease, POAC=Primary open angle glaucoma, PACG= Primary angle closure glaucoma, PAC= Primary angle closure, PACS= Primary angle closure suspect, BMI=Body mass index, PVI=Presenting visual impairment, VCDR= vertical cup-to-disc ratio，CCT=central cornea thickness, IOP=Intraocular pressure.

Table 3 Cox Proportional Hazards Models of 10 Year Mortality Categorized by Angle Status.

	Participants, N	Died, N	Mortality Rate, %(95%CI)	HR (95% CI)		
				Univariable	Age and Gender Adjusted	Multivariable Adjusted†
Angle Status						
Normal	1153	235	20.4 (18.1,22.8)	Reference [1]	Reference [1]	Reference [1]
PAC	33	10	30.3 (15.6,48.7)	1.41(0.75,2.65)	1.27 (0.67,2.39)	0.85 (0.37,1.94)
PACS	136	43	31.6 (23.9,40.1)	1.59(1.15,2.19)	1.32 (0.95,1.83)	1.27 (0.84,1.90)
PACG	21	10	47.6 (25.7,70.2)	2.63(1.40,4.95)	2.15 (1.14,4.04)	1.60 (0.70,3.61)
PACD (PAC+PACS+PACG)	190	63	33.2 (26.5,40.3)	1.74(1.32,2.30)	1.46 (1.10,1.95)	1.25 (0.87,1.79)
POAG	29	8	27.6 (12.7,47.2)	1.31(0.65,2.65)	0.74 (0.36,1.49)	0.70 (0.32,1.51)
Any glaucoma (PACG+POAG)	50	18	36.0 (22.9,50.8)	1.85(1.15,2.97)	1.18 (0.73,1.91)	0.96 (0.54,1.71)

Abbreviations: PAC= Primary angle closure, PACS= Primary angle closure suspect, PACG= Primary angle closure glaucoma, PACD=Primary angle closure disease, POAG=Primary open angle glaucoma, HR=Hazard ratio, CI=Confidence interval.

† Adjusted for age, gender, education, income, body mass index, presenting visual impairment, history of diabetes and hypertension.

Table 4 Cox Proportional Hazards Models of 10 Year Mortality Categorized by IOP and VCDR.

	Participants, N	Died, N	Mortality Rate, %(95%CI)	HR (95% CI)		
				Univariable	Age and Gender Adjusted	Multivariable Adjusted†
IOP						
Unit increase	-	-	-	1.02(0.99,1.05)	1.02 (0.99,1.05)	1.02 (0.99,1.05)
10~21	1267	272	21.5(19.2,23.8)	Reference [1]	Reference [1]	Reference [1]
<10	43	12	27.9(15.3,43.7)	1.32(0.74,2.35)	1.16 (0.68,1.99)	0.91 (0.44,1.89)
>21mmHg	50	14	28.0(16.2,42.5)	1.34(0.78,2.28)	0.97 (0.48,1.97)	0.97 (0.49,1.91)
VCDR						
Unit increase	-	-	-	3.86(2.05,7.26)	1.76 (0.94,3.30)	1.59 (0.74,3.46)
≤0.3	453	68	15.0(11.8,18.6)	Reference [1]	Reference [1]	Reference [1]
>0.3	867	209	24.1(21.3,27.1)	1.71(1.30,2.25)	1.53 (1.16,2.01)	1.60 (1.11,2.33)

Abbreviations: IOP=Intraocular pressure, VCDR=Vertical cup disc ration, HR= Hazard ratio, CI=confidence interval.

† Adjusted for age, gender, education, income, body mass index, presenting visual impairment, history of diabetes and hypertension.

Supplement Table 1 Cox Proportional Hazards Models of 10 Year Mortality Categorized by VCDR of different cut-off.

	Participants, N	Died, N	Mortality Rate, %(95%CI)	HR (95% CI)		
				Univariable	Age and Gender Adjusted	Multivariable Adjusted†
VCDR						
≤0.5	1012	197	19.5(17.1,22.0)	Reference [1]	Reference [1]	Reference [1]
>0.5	308	80	26.0(21.2,31.2)	1.37(1.06,1.78)	1.10 (0.84,1.43)	1.11 (0.82,1.51)
VCDR						
<0.7	1160	229	19.7(17.5,22.2)	Reference [1]	Reference [1]	Reference [1]
≥0.7	160	48	30.0(23.0,37.7)	1.62(1.18,2.20)	1.16 (0.84,1.59)	1.15 (0.80,1.67)

Abbreviations: IOP=Intraocular pressure, VCDR=Vertical cup disc ration, HR= Hazard ratio, CI=confidence interval.

† Adjusted for age, gender, education, income, body mass index, presenting visual impairment, history of diabetes and hypertension

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-9*
Bias	9	Describe any efforts to address potential sources of bias	7-9

Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12

		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of Glaucoma with Ten-Year Mortality in a Population-based Longitudinal Study in Urban Southern China: The Liwan Eye Study

Running tilt: Glaucoma and mortality

Research question: The association between glaucoma and ten-year mortality in an adult population in China

Study design: Population-based cohort study

Authors

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Tables: 4 **Figure:** 1

Abstract

Objectives: To investigate the association between glaucoma and ten-year mortality rate in an adult population in China.

Design: Population-based cohort study.

Setting: The Liwan Eye Study.

Participants: 1405 baseline participants aged 50 years and older were invited to attend a ten-year follow-up examination.

Primary and secondary outcome measures: The International Society of Geographic and Epidemiologic Ophthalmology criteria was used to define glaucoma. Detailed information of mortality was confirmed using the Chinese Centre for Disease Control and Prevention. Presenting visual impairment (PVI) was defined as a presenting visual acuity of less than 20/40 in the better-seeing eye. The ten-year mortality rates were compared using the log-rank test. Cox proportional hazards regression models were used to investigate the association between glaucoma and mortality.

Results: A total of 1372(97.7%) participants with available gonioscopic data were included in the analysis. Of these, 136(9.9%), 33(2.4%) and 21(1.5%) participants had primary angle closure suspect (PACS), primary angle closure (PAC) and primary angle closure glaucoma (PACG), and 29(2.1%) had primary open angle glaucoma (POAG). After ten years, 306 (22.3%) participants were deceased. The ten-year mortality was significantly associated with PACG(HR,2.15,95%CI:1.14-4.04) but not associated with PAC, PACS and POAG when age and gender were adjusted for. This association was no longer statistically significant when co-variables, such as income, education, body mass index, PVI, history of diabetes and hypertension, were adjusted for. Larger vertical cup-to-disc ratio (VCDR>0.30) was only a significant risk factor in multivariable analysis

(HR,1.60;95%CI,1.11-2.33).

Conclusions: PACG was significantly associated with higher long-term mortality but this association was likely to be confounded by other systemic risk factors. VCDR>0.3 was the only independent predictor, implying that it may be a marker of ageing and frailty.

Patient and Public Involvement Statement: No patients and public were involved in the design and process of this study.

Key words: Glaucoma; Mortality; China; Cox proportional hazards regression model

Strengths and limitations of this study

1.The present study was a population-based cohort study which utilized a standardized study protocol

2. The International Society of Geographic and Epidemiologic Ophthalmology criteria was used to define glaucoma

3. Study limitations include the following: 1) small number of patients with glaucoma;2) several important confounding factors, such as smoking status were not available.

Introduction

Glaucoma is one of the leading causes of irreversible visual impairment (VI) and blindness worldwide, affecting approximately 64.3 million people .[1] It has been estimated that the number of people diagnosed with glaucoma in China was 13.1 million in 2015, more than half of which were diagnosed with primary angle closure glaucoma(PACG).[2] With the current ageing population, this number is expected to reach 15.2 million by 2050.[2]

In addition to its impact on vision and quality of life, some studies have reported that patients with glaucoma have higher rates of mortality,[3-6] while others found no association,[7-18] Disparate findings have led to controversies regarding the risk of premature mortality of patients with glaucoma. Similarly, inconsistent evidence has been observed regarding the association between levels of intraocular pressure (IOP), a well-established functional risk factor for glaucoma, and survival.[14, 17, 18] The relationship between mortality and vertical cup-to-disc ratio (VCDR), a robust structural indicator of glaucomatous loss of the neuroretinal rim, has been exclusively investigated in the Andhra Pradesh Eye Disease Study (APEDS), implying that nerve fiber loss may be a marker of ageing and frailty.[7] Of note, previous studies, mainly in white and black populations, investigated the relationship between primary open angle glaucoma (POAG), elevated IOP and long-term survival.[8-10, 12, 14, 15, 18, 19] In comparison, few studies have been conducted in Asian populations.[3, 4, 7, 11, 13, 16] Furthermore, dominant subtypes, clinical presentations and the underlying pathogenesis of glaucoma in Asian populations vary from those in white and black populations.[20, 21] A better understanding of the relationship between different subtypes of glaucoma (POAG and primary angle closure disease (PACD)), level of IOP, VCDR and risk of mortality may provide insights into the potential mechanisms and clinical management of glaucoma.

Therefore, the aim of this study was to explore the relationship between different types of glaucoma, level of IOP, VCDR and ten-year mortality in an adult population in southern urban China.

Methods

Study Population

A detailed description of the methodology utilized in the Liwan Eye Study has been described previously.[22] Briefly, the Liwan Eye Study was a population-based cohort study that commenced in 2003 with a five-year follow-up (2008 to 2009) and a ten-year follow-up (2013), both follow-up examinations followed an identical protocol. At baseline, 75.4% (1405 of 1864) of eligible participants underwent a comprehensive eye examination and a questionnaire regarding income, education, and medical history. All participants in the baseline study were invited back for the five- and ten-year follow-up examinations. A total of 924 participants (75.0% of survivors, 79.1% of eligible participants) returned for the five-year examination and 791 (73.8% of survivors, 86.2% of eligible participants) for the ten-year examination.

Ethical approval for the study was obtained from the Zhongshan University Ethics Review Board, and the Research Governance Committee of Moorfields Eye Hospital, London. The study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from all participants.

Study procedure

All participants had their presenting visual acuity (PVA) tested using an Early

Treatment Diabetic Retinopathy Study (ETDRS) vision chart whilst wearing their habitual refractive correction. Best-corrected visual acuity (BCVA) was measured for those with PVA ≤ 20/40 in either eye. Presenting visual impairment (PVI) was defined as PVA less than 20/40 in the better-seeing eye. The IOP was measured before mydriasis by a handheld tonometer (Tonopen; Mentor, Norwell, Massachusetts, USA) with three consecutive measurements of an achieved standard error of <5%. Central cornea thickness (CCT) was evaluated using an ultrasound pachymetry (Echoscan US1800; Nidek,Corp). Height and weight were measured without shoes, using a standard calibrated scale. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in centimeters and was divided into three groups: underweight (BMI <18.5 kg/m^2), normal to overweight (18.5 to30 kg/m^2), or obese (BMI ≥ 30.0 kg/m^2). Diabetes mellitus (DM) and hypertension were based on self-reported history of a diagnosis and/or previous medication use.

Slit-lamp examination (TopconSL-8Z, Tokyo, Japan) with a 78-diopter lens was used to identify abnormalities of the anterior segment and posterior segment by an experienced ophthalmologist (MH). Detailed information of the gonioscopic examination in the Liwan Eye Study has been described previously.[22] Briefly, all participants underwent slit lamp based static and dynamic gonioscopy with a Goldmann-type, one-mirror lens (Haag Streit, Bern, Switzerland) at 25x magnification by the same experienced specialist-trained ophthalmologist (MH). Narrow angle and open angle were stratified by status of the iris insertion and recorded using five categories by the Shaffer system. [23]According to the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) classification, primary angle closure suspect (PACS) was defined as simply an angle in which ≥270°of the

pigmented trabecular meshwork cannot be seen without evidence of trabecular obstruction and glaucomatous damage. Primary angle closure (PAC) was defined as eyes with PACS and features of peripheral anterior synechiae, elevated IOP, iris wholing, or excessive pigment deposition on the trabecular surface, but no evidence of glaucomatous damage. Primary angle closure glaucoma (PACG) was defined as eyes with PAC and evidence of glaucomatous damage. Participants with PACS, PAC or PACG were grouped as PACD.

The optic disc was assessed using a 78-D lens at 16x magnification. The VCDR was used as key indicator of structural glaucomatous change. Visual field (VF) assessment was performed in those with a VCDR of ≥0.7(97.5th percentile of the Liwan Eye Study) in either eye, VCDR asymmetry ≥0.2 or IOP of ≥21 mm Hg on a subsequent day. The definition of glaucoma was based on three levels of evidence using ISGEO criteria. The division of POAG and PACG was based on the gonioscopic results of narrow angle or open angle. If glaucoma status or VCDR were observed in both eyes, the eye with more severe status or larger VCDR value was used in the analysis.

Detailed data from the Chinese Centre for Disease Control and Prevention (CDC) were used to confirm the mortality of participants during the ten-year follow-up period. After providing the CDC with a list of names, age, year of birth, gender and latest address for the participants suspected of having passed away, based on which researchers at the CDC provided a corresponding list of “matched” deaths with dates and causes. The causes of death recorded by the CDC were documented on the death certificates using the International Classification of Diseases, Ninth Revision.

Statistical analysis

All statistical analyses were performed using Stata (ver. 10.0; Stata Corp, College Station, TX). The student's t-test was used to compare continuous variables, while Pearson chi squire or Fisher's exact test for the comparison of categorical data. Survival times were calculated for each participant from the date of baseline examinations to the date of death or April 30, 2014. Univariable and multivariable Cox proportional hazard regression models were used to test the associations between mortality and baseline PACS, PAC, PACG, POAG, IOP and VCDR after adjusting for baseline characteristics of age, gender, education level, family income, history of diabetes and hypertension and PVI. Analysis of IOP and VCDR were based on both continuous and categorical level. IOP was divided into three categorical groups: 10-21mmHg (reference group), <10mmHg and >21 mmHg. The lowest quartile of VCDR (≤0.3), the third quartile of VCDR in this population (≤0.5) and VCDR of < 0.7 (97.5th percentile of the Liwan Eye Study) were used as the reference group to assess associations of different VCDR cut-offs with long-term survival. Hazard ratios (HR) and 95% confidence intervals (CI) were given. A proportional hazard test was used to check the assumption of cox proportional hazards model, and the log-rank test was used to compare different groups with respect to their survival distributions.

Results

Of the 1405 participants at baseline, 33 were excluded (30 without gonioscopic data, 3 with secondary glaucoma and 1 with un-classified reason du to cataract surgery), leaving 1372 participants with complete data available for analysis. Among the 1372 participants, the prevalence of PACS, PAC,

PACG, and POAG was 9.9% (136 participants), 2.4% (33 participants), 1.5% (21 participants), and 2.1% (29 participants), respectively (Figure1). Compared to the 1153 normal participants, those with PACD were more likely to be older (P<0.001), female (P=0.001), underweight (P<0.001), of a lower level of family income (P=0.005) and have a higher proportion of PVI (P<0.001). There were no statistically significant differences between groups in terms of level of education, hypertension, diabetes, CCT and IOP. Compared to the 1,153 normal participants, those with POAG tended to be older (P=0.003), male (P=0.003) and had a higher proportion of PVI (P=0.001) (Table 1).

By the end of April 2014 (median follow-up length: 9.38 years; range: 0.15-10.4), 306 (22.3%) of the 1,372 participants passed away, 294 (21.4%) did not return for re-examination because they declined participation (126) , relocated (122) or were uncontactable (41), leaving 777(56.6%) at the ten-year follow-up examination. Detailed follow-up information can be found in Figure 1. Those who passed away tended to be older (P<0.001), male (P<0.001), have a lower level of educational attainment (P=0.001), lower family income (P<0.001), higher proportion of PVI (P<0.001), larger VCDR (P<0.001) and be underweight (P=0.009). The medical history of hypertension and diabetes, CCT and mean IOP value were similar between the two groups (Table 2).

Among the 1153 participants without PACD or POAG, 235 (20.4%, 95%CI=18.1, 22.8%) passed away during the ten-year follow up period. The ten-year mortality rate of the 1153 participants was significantly lower than those with PACS (43/136, 31.6%, 95%CI= 23.9, 40.1%), PAC (10/33, 30.3%, 95%CI= 15.6, 48.7%), PACG (10/21, 47.6%, 95%CI=25.7, 70.2%), and POAG

(8/29, 27.6%, 95%CI= 12.7, 47.2%). The age and gender adjusted cox proportional hazards model showed that the presence of PACG (HR=2.15, 95% CI=1.14, 4.04), PACD (HR=1.46, 95% CI=1.10, 1.95) and a VCDR of more than 0.3 (HR=1.53, 95% CI=1.16, 2.01) were significantly associated with a higher risk of mortality. No association was found between mortality and PACS, PAC, POAG and level of IOP. After adjusting for age, gender, education, income, history of diabetes and hypertension, BMI and PVI, the significant association between VCDR of more than 0.3 and poorer survival rate was still observed (HR=1.60, 95% CI=1.11, 2.33) (Table 3 and Table 4). A strong associations between ten year mortality and a VCDR>0.5 (HR=1.37, 95% CI=1.06, 1.78) and VCDR≥0.7 (HR=1.62, 95% CI=1.18, 2.20) were found in the univariable analysis, whereas these associations disappeared after adjusting for confounders (all P>0.05, Supplement Table 1).

Discussion

In this population-based cohort study, we found a higher crude mortality rate among patients with POAG and any form of PACD (ranging from 7.2% to 27.2%). However, this difference was not replicated after multivariable confounders were adjusted for. Level of IOP was not significantly associated with an increased risk of ten-year mortality in the multivariable model, while VCDR of more than 0.3 was an independent predictor of long-term poor survival.

Controversy still exists around the association between POAG and the increased risk of mortality.[3-10, 12, 14-16, 18, 19] Almost 50 years ago, Egge et al found a decreased 30-year survival rate for patients with glaucoma in Norway. This finding was more pronounced among men using acetazolamide.[6] Results

of the National Health Interview Survey (NHIS) 1986-1994 also supported the finding that glaucoma was related to an increased risk of all-cause and cardiovascular disease mortality among adults residing in the United States.[5] However, the glaucoma-mortality association in the NHIS is likely to have been impacted by recall bias (self-reported definition of glaucoma), misclassification error and underestimation of glaucoma cases. Furthermore, the diagnostic methods, definition and treatments of glaucoma have changed over the past five decades, making its findings less generalizable to today's glaucoma patients. More recent studies are in favor of the finding that POAG is not significantly associated with long-term survival.[3, 4,7-10, 12, 14-16, 18] The non-significant relationship in these studies are in agreement with the findings of our study. Differences in ethnicity, age distribution, study design, length of follow-up, definition of glaucoma, and confounding variables adjusted for in the multivariate model may explain the inconsistent results between studies. Alternatively, the small number of patients with POAG in the current study (n=29) may also explain the lack of association between POAG and ten-year mortality. However, a recent meta-analysis of observational studies[17] supported the finding of a non-significant relationship between POAG and risk of mortality.

Few studies have explored the relationship between different types of PACD and mortality. Similar to the current study, previously investigations have reported that the presence of PACD was not an independent risk factor for all-cause mortality.[7, 11, 13, 16] Thus far, only five-year data from the Beijing Eye Study has reported that the presence of PACG was related to an increased risk of mortality using multivariate analysis.[3, 4] Interestingly, the ten-year data from the Beijing Eye Study found that mortality was not significantly associated with PACG.[16] Neither the Tanjong Pagar Study[11] or the Singapore

Malay Eye Study (SiMES)[13] found significantly reduced survival among those with glaucoma. In the current study, we found that PACG was significantly associated with ten-year mortality in the age and gender adjusted model, but this significant association was not found in the multivariate model. This is likely due to other confounding factors not accounted for and the relatively small sample size.

The results of this study found a non-significant association between the level of IOP and ten-year mortality rate. Previous reports on the relationship between all-cause mortality and elevated IOP have been inconsistent.[7, 14, 18, 19] Excess all-cause mortality associated with ocular hypertension was found in the Barbados Eye Study and the Framingham Study,[18] while the APEDS[7] and a Swedish study[14] found no statistically significant association between elevated IOP and mortality risk. The APEDS was the only study to explore the association between VCDR and all-cause mortality. Consistent with the APEDS's finding that increasing VCDR was a predictor of ten-year mortality,[7] we also reported a significantly increased risk of mortality among participants with VCDR of more than 0.3. Considering that previous studies have indicated that global retinal nerve fiber layer decreased significantly with age and larger VCDR,[24, 25] one can speculate that the potential mechanism underlying the VCDR-mortality association may be caused by retinal nerve fiber layer thinning, a marker of ageing and frailty. Furthermore, the close relationship between neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease) and glaucoma, and the strong link between retinal nerve fiber layer thinning and brain pathology adds weight to our speculation.[26-29] The non-significant association of other cut-offs, or linear of VCDR with all-cause mortality after adjusting for confounders might be due to the small sample size or non-linear relationship in our study. Alternatively, we can only

speculate that VCDR of less than 0.3 (i.e., sufficient retinal nerve fibre layer) which represent physiological process of aging or neurodegeneration might be the threshold for better survival. Further studies with a larger study sample are needed to investigate the association between VCDR, retinal nerve fiber layer thickness and mortality.

Even though the mechanisms underlying the association between glaucoma/ocular hypertension-mortality is still unclear, it has been speculated that increased risk of mortality among patients with glaucoma or ocular hypertension might be caused by IOP-lowering treatment. Glaucoma-mortality association has been found to be more pronounced among men using acetazolamide.[6] The excess mortality linked to timolol maleate treatment for POAG found in the Barbados Eye Study[18] was also parallel to the hypothesis of this study. In the BMES, a dose-dependent pattern was observed in the association between duration of timolol maleate use and increased risk of cardiovascular disease mortality. In addition, previous studies verified the adverse effects of IOP-lowering treatments, including congestive heart failure, raised blood pressure and adverse respiratory effects.[30, 31] However, the dose-dependent pattern observed in the BMES may be due to detection bias. Approximately 50-90% of glaucoma patients remain undiagnosed.[7, 32] Participants in poorer health are more likely to access health care services and therefore have their glaucoma diagnosed and treated. The suggestion that detection bias is a cause of variable findings was further verified by the similar mortality rates between treated and untreated glaucoma patients in multicenter randomized glaucoma treatment trials (Early Manifest Glaucoma Trial and Ocular Hypertension Treatment Study) and the observational Rotterdam study.[33-35] Even these two studies concluded that the use of glaucoma medications was associated with a reduced risk of mortality.[36, 37]

Future investigations are required to assess this association further.

The strengths of the present study included the population-based study design, high participation rate, long-term follow-up, and standardized definition of glaucoma used. Of note, the present study was limited by the following points. Firstly, the small number of patients with glaucoma may explain the non-significant association between different types of glaucoma and mortality. Second, several important confounding factors, such as smoking status were not available in the present study. Nevertheless, the additional adjustment for these important confounding factors may further attenuate the magnitude of statistical significance and again verify the robustness of our results. Third, lack of data on the causes of death prevented the possibility of exploring the association between glaucoma and specific-cause mortality. Previous studies have reported a significant association between glaucoma and cardiovascular disease mortality.[5, 38] Fourthly, the fact that only participants with suspect glaucoma (VCDR of ≥0.7 in either eye (97.5th percentile of the Liwan Eye Study population), VCDR asymmetry ≥0.2 or IOP of ≥21 mm Hg) underwent VF assessment may underestimate the prevalence of glaucoma because participants with early glaucomatous changes may be missed. However, previous ocular history and IOP measurements were collected for each participant, possibly lowering the risk of underestimation. Fifthly, the relationship between changes in glaucoma related parameters and long-term survival were unavailable due to insufficient data and limited follow-up times. Finally, we did not collect information on utilization of IOP-lowering treatment. Further studies are required to investigate the relationship between IOP-lowering treatment and long-term survival.

In conclusion, our findings suggest there is a higher level of crude mortality among patients with POAG, PACS or PAC. However, this difference was unable to be replicated after multivariable confounders were adjusted for. PACG was significantly associated with ten-year mortality in the age and gender adjusted model, but this significant association disappeared in the multivariable model. Level of IOP was not significantly associated with increased risk of ten-year mortality, while VCDR of more than 0.3 was an independent predictor of long-term survival. Further studies are needed to confirm these findings and to explore the association between different subtypes and treatments of glaucoma with long-term survival.

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Figure legend:

Figure1 Flow chart showing the enrollment and follow-ups of participants in the Liwan Eye Study

Table 1 Baseline Characteristics of participants with POAG, PACG, PAC and PACS.

Basic characteristics	Normal, N (%)	PACD				POAG, N (%)
		PACS, N	PAC, N (%)	PACG, N	Total, N	
Total number (%)	1153(100)	136 (100)	33 (100)	21 (100)	190 (100)	29 (100)
Age (%)						
50-59	440 (38.2)	17 (12.5)	5 (15.2)	0 (0)	22 (11.6)	4 (13.8)
60-69	328 (28.5)	46 (33.8)	12 (36.4)	5 (23.8)	63 (33.2)	7 (24.1)
+70	385 (33.4)	73 (53.7)	16 (48.5)	16 (76.2)	105 (55.3)	18 (62.1)
Female (%)	639 (55.4)	95 (69.9)	26 (78.8)	13 (61.9)	134 (70.5)	8 (27.6)
No more than middle school	809 (79.3)	93 (79.5)	19 (63.3)	12 (70.6)	124 (75.6)	22 (78.6)
Income less than 1000RMB	585 (72.7)	78 (82.1)	22 (88.0)	12 (92.3)	112 (84.2)	19 (70.4)
BMI (kg/m^2)						
Normal (18.5-30.0)	716 (91.6)	79 (85.0)	16 (72.7)	11 (84.6)	106 (82.8)	23 (88.5)
Under weight (<18.5)	39 (4.99)	14 (15.1)	3 (13.6)	1 (7.69)	18 (14.1)	3 (11.5)
Over weight (≥30.0)	27 (3.45)	0 (0)	3 (13.6)	1 (7.69)	4 (3.13)	0 (0)
Hypertension (%)	416 (40.1)	61 (45.9)	15 (45.5)	10 (50.0)	86 (46.2)	16 (57.1)
Diabetes (%)	105 (10.1)	16 (12.0)	3 (9.09)	4 (20.0)	23 (12.4)	3 (10.7)

PVI (%)	228 (19.8)	45 (33.3)	12 (36.4)	10 (47.6)	67 (35.5)	13 (44.8)
CCT(μm)	541.7±33.2	535.5±33.4	542.9±29.8	550.4±26.9	538.4±32.5	542.5±35.2
IOP (mmHg, SD)	15.2±3.04	15.1±2.88	14.8±4.25	19.4±5.36	15.5±3.71	15.8±2.87

Abbreviations: PACD=Primary angle closure disease, POAC=Primary open angle glaucoma, PACG= Primary angle closure glaucoma, PAC= Primary angle closure, PACS= Primary angle closure suspect, BMI=Body mass index, PVI=Presenting visual impairment, CCT=central cornea thickness, IOP=Intraocular pressure

Table 2 Distribution of Basic Characters Associated with Mortality at Baseline Examination.

Basic Factors	Died, N (%)	Alive, N (%)	P-value
Total number (%)	306 (100)	1066 (100)	
Age (%)			<0.001
50-59	23 (7.52)	443 (41.6)	
60-69	66 (21.6)	332 (31.1)	
+70	217 (70.9)	291 (27.3)	
Female (%)	147 (48.0)	634 (59.5)	<0.001
No more than middle school	155 (67.7)	800 (81.4)	<0.001
Income less than 1000RMB	173 (83.2)	543 (71.7)	0.001
BMI (kg/m^2)			0.009
Normal (18.5-30.0)	169 (85.8)	676 (91.5)	
Under weight (<18.5)	22 (11.2)	38 (5.14)	
Over weight (≥30.0)	6 (3.05)	25 (3.38)	
Hypertension (%)	111 (44.4)	407 (40.6)	0.277
Diabetes (%)	33 (13.2)	98 (9.79)	0.120
PVI (%)	120 (39.5)	188 (17.6)	<0.001
VCDR(mean±SD)	0.49±0.18	0.44±0.17	<0.001
CCT(μm)	540.3±35.3	541.5±32.5	0.582
IOP (mmHg, SD)(mean±SD)	15.1±3.32	15.3±3.08	0.495

Abbreviations: PACD=Primary angle closure disease, POAC=Primary open angle glaucoma, PACG= Primary angle closure glaucoma, PAC= Primary angle closure, PACS= Primary angle closure suspect, BMI=Body mass index, PVI=Presenting visual impairment, VCDR= vertical cup-to-disc ratio，CCT=central cornea thickness, IOP=Intraocular pressure.

Table 3 Cox Proportional Hazards Models of ten-Year Mortality Categorized by Angle Status.

	Participants, N	Died, N	Mortality Rate, %(95%CI)	HR (95% CI)					
				Univariable	P-value	Age and Gender Adjusted	P-value	Multivariable Adjusted†	P-value
Angle Status									
Normal	1153	235	20.4 (18.1,22.8)	Reference [1]		Reference [1]		Reference [1]	
PAC	33	10	30.3 (15.6,48.7)	1.41(0.75,2.65)	0.284	1.27 (0.67,2.39)	0.463	0.85 (0.37,1.94)	0.702
PACS	136	43	31.6 (23.9,40.1)	1.59(1.15,2.19)	0.005	1.32 (0.95,1.83)	0.099	1.27 (0.84,1.90)	0.253
PACG	21	10	47.6 (25.7,70.2)	2.63(1.40,4.95)	0.003	2.15 (1.14,4.04)	0.018	1.60 (0.70,3.61)	0.263
PACD (PAC+PACS+PACG	190	63	33.2 (26.5,40.3)	1.74(1.32,2.30)	<0.001	1.46 (1.10,1.95)	0.009	1.25 (0.87,1.79)	0.221
POAG	29	8	27.6 (12.7,47.2)	1.31(0.65,2.65)	0.449	0.74 (0.36,1.49)	0.395	0.70 (0.32,1.51)	0.359
Any glaucoma (PACG+POAG)	50	18	36.0 (22.9,50.8)	1.85(1.15,2.97)	0.012	1.18 (0.73,1.91)	0.505	0.96 (0.54,1.71)	0.877

Abbreviations: PAC= Primary angle closure, PACS= Primary angle closure suspect, PACG= Primary angle closure glaucoma, PACD=Primary angle closure disease, POAG=Primary open angle glaucoma, HR=Hazard ratio, CI=Confidence interval.

† Adjusted for age, gender, education, income, body mass index, presenting visual impairment, history of diabetes and hypertension.

Table 4 Cox Proportional Hazards Models of ten-Year Mortality Categorized by IOP and VCDR.

	Participants, N	Died, N	Mortality Rate, %(95%CI)	HR (95% CI)					
				Univariable	P-value	Age and Gender Adjusted	P-value	Multivariable Adjusted†	P-value
IOP									
Unit increase	-	-	-	1.02(0.99,1.05)	0.580	1.02 (0.99,1.05)	0.262	1.02 (0.99,1.05)	0.203
10~21	1267	272	21.5(19.2,23.8)	Reference [1]		Reference [1]		Reference [1]	
<10	43	12	27.9(15.3,43.7)	1.32(0.74,2.35)	0.349	1.16 (0.68,1.98)	0.680	0.91 (0.44,1.89)	0.798
>21mmHg	50	14	28.0(16.2,42.5)	1.34(0.78,2.28)	0.291	0.97 (0.48,1.97)	0.584	0.97 (0.49,1.91)	0.935
VCDR									
Unit increase	-	-	-	3.86(2.05,7.26)	<0.001	1.76 (0.94,3.30)	0.076	1.59 (0.74,3.46)	0.238
≤0.3	453	68	15.0(11.8,18.6)	Reference [1]		Reference [1]		Reference [1]	
>0.3	867	209	24.1(21.3,27.1)	1.71(1.30,2.25)	<0.001	1.53 (1.16,2.01)	0.002	1.60 (1.11,2.33)	0.011

Abbreviations: IOP=Intraocular pressure, VCDR=Vertical cup disc ration, HR= Hazard ratio, CI=confidence interval.

† Adjusted for age, gender, education, income, body mass index, presenting visual impairment, history of diabetes and hypertension.

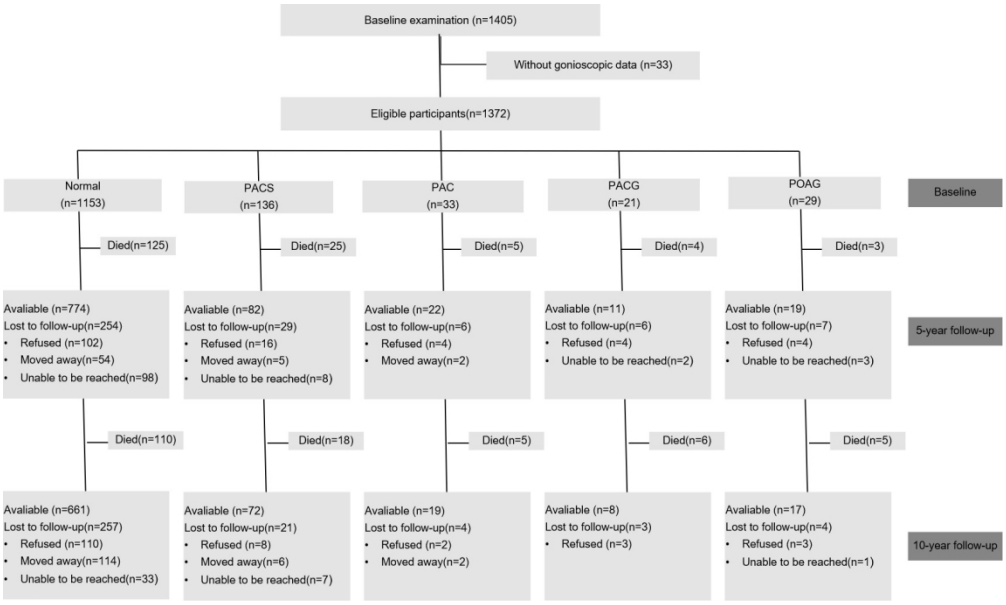

Figure1 Flow chart showing the enrollment and follow-ups of participants in the Liwan Eye Study

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Supplement Table 1 Cox Proportional Hazards Models of ten-Year Mortality Categorized by VCDR of different cut-off.

	Participants, N	Died, N	Mortality Rate, %(95%CI)	HR (95% CI)					
				Univariable	P-value	Age and Gender Adjusted	P-value	Multivariable Adjusted†	P-value
VCDR									
≤0.5	1012	197	19.5(17.1,22.0)	Reference [1]		Reference [1]		Reference [1]	
>0.5	308	80	26.0(21.2,31.2)	1.37(1.06,1.78)	0.016	1.10 (0.84,1.43)	0.500	1.11 (0.82,1.51)	0.490
VCDR									
<0.7	1160	229	19.7(17.5,22.2)	Reference [1]		Reference [1]		Reference [1]	
≥0.7	160	48	30.0(23.0,37.7)	1.62(1.18,2.20)	0.003	1.16 (0.84,1.59)	0.367	1.15 (0.80,1.67)	0.445

Abbreviations: IOP=Intraocular pressure, VCDR=Vertical cup disc ration, HR= Hazard ratio, CI=confidence interval.

† Adjusted for age, gender, education, income, body mass index, presenting visual impairment, history of diabetes and hypertension

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-9*
Bias	9	Describe any efforts to address potential sources of bias	7-9
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	10-11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of Glaucoma with Ten-Year Mortality in a Population-based Longitudinal Study in Urban Southern China: The Liwan Eye Study

Running tilt: Glaucoma and mortality

Research question: The association between glaucoma and ten-year mortality in an adult population in China

Study design: Population-based cohort study

Authors

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Tables: 4 **Figure:** 2

Supplement Table:1

Abstract

Objectives: To investigate the association between glaucoma and ten-year mortality rate in an adult population in China.

Design: Population-based cohort study.

Setting: The Liwan Eye Study, China.

Participants: 1405 baseline participants aged 50 years and older were invited to attend a ten-year follow-up examination.

Primary and secondary outcome measures: The International Society of Geographic and Epidemiologic Ophthalmology criteria was used to define glaucoma. Detailed information of mortality was confirmed using the Chinese Centre for Disease Control and Prevention. Presenting visual impairment (PVI) was defined as a presenting visual acuity of less than 20/40 in the better-seeing eye. The ten-year mortality rates were compared using the log-rank test. Cox proportional hazards regression models were used to investigate the association between glaucoma and mortality.

Results: A total of 1372(97.7%) participants with available gonioscopic data were included in the analysis. Of these, 136(9.9%), 33(2.4%) and 21(1.5%) participants had primary angle closure suspect (PACS), primary angle closure (PAC) and primary angle closure glaucoma (PACG), and 29(2.1%) had primary open angle glaucoma (POAG). After ten years, 306 (22.3%) participants were deceased. The ten-year mortality was significantly associated with PACG (HR, 2.15,95%CI:1.14-4.04,P=0.018) but not associated with PAC (HR,1.27,95%CI:0.67-2.39, P=0.463), PACS (HR,1.32,95%CI:0.95-1.83, P=0.099) and POAG (HR, 0.74, 95%CI:0.36-1.49, P=0.395) when age and gender were adjusted for. This association was no longer statistically significant (HR,1.60, 95%CI:0.70-3.61, P=0.263) when co-variables, such as income, education, body mass index, PVI, history of

diabetes and hypertension, were adjusted for. Larger vertical cup-to-disc ratio (VCDR>0.30) was only a significant risk factor in multivariable analysis (HR, 1.60,95%CI:1.11-2.33, P=0.011).

Conclusions: PACG was significantly associated with higher long-term mortality but this association was likely to be confounded by other systemic risk factors. VCDR>0.3 was the only independent predictor, implying that it may be a marker of ageing and frailty.

Patient and Public Involvement Statement: No patients and public were involved in the design and process of this study.

Key words: Glaucoma; Mortality; China; Cox proportional hazards regression model

Strengths and limitations of this study

1.The present study was a population-based cohort study which utilized a standardized study protocol

2. The International Society of Geographic and Epidemiologic Ophthalmology criteria was used to define glaucoma

3. Study limitations include the following: 1) small number of patients with glaucoma;2) several important confounding factors, such as smoking status were not available.

Introduction

Glaucoma is one of the leading causes of irreversible visual impairment (VI) and blindness worldwide, affecting approximately 64.3 million people .[1] It has been estimated that the number of people diagnosed with glaucoma in China was 13.1 million in 2015, more than half of which were diagnosed with primary angle closure glaucoma(PACG).[2] With the current ageing population, this number is expected to reach 15.2 million by 2050.[2]

In addition to its impact on vision and quality of life, some studies have reported that patients with glaucoma have higher rates of mortality,[3-6] while others found no association,[7-18] Disparate findings have led to controversies regarding the risk of premature mortality of patients with glaucoma. Similarly, inconsistent evidence has been observed regarding the association between levels of intraocular pressure (IOP), a well-established functional risk factor for glaucoma, and survival.[14, 17, 18] The relationship between mortality and vertical cup-to-disc ratio (VCDR), a robust structural indicator of glaucomatous loss of the neuroretinal rim, has been exclusively investigated in the Andhra Pradesh Eye Disease Study (APEDS), implying that nerve fiber loss may be a marker of ageing and frailty.[7] Of note, previous studies, mainly in white and black populations, investigated the relationship between primary open angle glaucoma (POAG), elevated IOP and long-term survival.[8-10, 12, 14, 15, 18, 19] In comparison, few studies have been conducted in Asian populations.[3, 4, 7, 11, 13, 16] Furthermore, dominant subtypes, clinical presentations and the underlying pathogenesis of glaucoma in Asian populations vary from those in white and black populations.[20, 21] A better understanding of the relationship between different subtypes of glaucoma (POAG and primary angle closure disease (PACD)), level of IOP, VCDR and risk of mortality may provide insights into the potential mechanisms and clinical management of glaucoma.

Therefore, the aim of this study was to explore the relationship between different types of glaucoma, level of IOP, VCDR and ten-year mortality in an adult population in southern urban China.

Methods

Study Population

A detailed description of the methodology utilized in the Liwan Eye Study has been described previously.[22] Briefly, the Liwan Eye Study was a population-based cohort study that commenced in 2003 with a five-year follow-up (2008 to 2009) and a ten-year follow-up (2013), both follow-up examinations followed an identical protocol. At baseline, 75.4% (1405 of 1864) of eligible participants underwent a comprehensive eye examination and a questionnaire regarding income, education, and medical history. All participants in the baseline study were invited back for the five- and ten-year follow-up examinations. A total of 924 participants (75.0% of survivors, 79.1% of eligible participants) returned for the five-year examination and 791 (73.8% of survivors, 86.2% of eligible participants) for the ten-year examination.

Ethical approval for the study was obtained from the Zhongshan University Ethics Review Board, and the Research Governance Committee of Moorfields Eye Hospital, London. The study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from all participants.

Study procedure

All participants had their presenting visual acuity (PVA) tested using an Early

Treatment Diabetic Retinopathy Study (ETDRS) vision chart whilst wearing their habitual refractive correction. Best-corrected visual acuity (BCVA) was measured for those with PVA ≤ 20/40 in either eye. Presenting visual impairment (PVI) was defined as PVA less than 20/40 in the better-seeing eye. The IOP was measured before mydriasis by a handheld tonometer (Tonopen; Mentor, Norwell, Massachusetts, USA) with three consecutive measurements of an achieved standard error of <5%. Central cornea thickness (CCT) was evaluated using an ultrasound pachymetry (Echoscan US1800; Nidek,Corp). Height and weight were measured without shoes, using a standard calibrated scale. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in centimeters and was divided into three groups: underweight (BMI <18.5 kg/m^2), normal to overweight (18.5 to30 kg/m^2), or obese (BMI ≥ 30.0 kg/m^2). Diabetes mellitus (DM) and hypertension were based on self-reported history of a diagnosis and/or previous medication use.

Slit-lamp examination (TopconSL-8Z, Tokyo, Japan) with a 78-diopter lens was used to identify abnormalities of the anterior segment and posterior segment by an experienced ophthalmologist (MH). Detailed information of the gonioscopic examination in the Liwan Eye Study has been described previously.[22] Briefly, all participants underwent slit lamp based static and dynamic gonioscopy with a Goldmann-type, one-mirror lens (Haag Streit, Bern, Switzerland) at 25x magnification by the same experienced specialist-trained ophthalmologist (MH). Narrow angle and open angle were stratified by status of the iris insertion and recorded using five categories by the Shaffer system. [23]According to the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) classification, primary angle closure suspect (PACS) was defined as simply an angle in which ≥270°of the

pigmented trabecular meshwork cannot be seen without evidence of trabecular obstruction and glaucomatous damage. Primary angle closure (PAC) was defined as eyes with PACS and features of peripheral anterior synechiae, elevated IOP, iris wholing, or excessive pigment deposition on the trabecular surface, but no evidence of glaucomatous damage. Primary angle closure glaucoma (PACG) was defined as eyes with PAC and evidence of glaucomatous damage. Participants with PACS, PAC or PACG were grouped as PACD.

The optic disc was assessed using a 78-D lens at 16x magnification. The VCDR was used as key indicator of structural glaucomatous change. Visual field (VF) assessment was performed in those with a VCDR of ≥0.7(97.5th percentile of the Liwan Eye Study) in either eye, VCDR asymmetry ≥0.2 or IOP of ≥21 mm Hg on a subsequent day. The definition of glaucoma was based on three levels of evidence using ISGEO criteria. The division of POAG and PACG was based on the gonioscopic results of narrow angle or open angle. If glaucoma status or VCDR were observed in both eyes, the eye with more severe status or larger VCDR value was used in the analysis.

Detailed data from the Chinese Centre for Disease Control and Prevention (CDC) were used to confirm the mortality of participants during the ten-year follow-up period. After providing the CDC with a list of names, age, year of birth, gender and latest address for the participants suspected of having passed away, based on which researchers at the CDC provided a corresponding list of “matched” deaths with dates and causes. The causes of death recorded by the CDC were documented on the death certificates using the International Classification of Diseases, Ninth Revision.

Statistical analysis

All statistical analyses were performed using Stata (ver. 10.0; Stata Corp, College Station, TX). The student's t-test was used to compare continuous variables, while Pearson chi squire or Fisher's exact test for the comparison of categorical data. Survival times were calculated for each participant from the date of baseline examinations to the date of death or April 30, 2014. Univariable and multivariable Cox proportional hazard regression models were used to test the associations between mortality and baseline PACS, PAC, PACG, POAG, IOP and VCDR after adjusting for baseline characteristics of age, gender, education level, family income, history of diabetes and hypertension and PVI. These confounding factors were chosen based on the previous evidence. [24-28] The significant association between PVI and long-term survival in this population have been reported previously. [29] Analysis of IOP and VCDR were based on both continuous and categorical level. IOP was divided into three categorical groups: 10-21mmHg (reference group), <10mmHg and >21 mmHg. The lowest quartile of VCDR (≤0.3), the third quartile of VCDR in this population (≤0.5) and VCDR of < 0.7 (97.5th percentile of the Liwan Eye Study) were used as the reference group to assess associations of different VCDR cut-offs with long-term survival. Hazard ratios (HR) and 95% confidence intervals (CI) were given. A proportional hazard test was used to check the assumption of cox proportional hazards model, and the log-rank test was used to compare different groups with respect to their survival distributions.

Results

Of the 1405 participants at baseline, 33 were excluded (30 without gonioscopic data, 3 with secondary glaucoma and 1 with un-classified reason

du to cataract surgery), leaving 1372 participants with complete data available for analysis. Among the 1372 participants, the prevalence of PACS, PAC, PACG, and POAG was 9.9% (136 participants), 2.4% (33 participants), 1.5% (21 participants), and 2.1% (29 participants), respectively (Figure1). Compared to the 1153 normal participants, those with PACD were more likely to be older (P<0.001), female (P=0.001), underweight (P<0.001), of a lower level of family income (P=0.005) and have a higher proportion of PVI (P<0.001). There were no statistically significant differences between groups in terms of level of education, hypertension, diabetes, CCT and IOP. Compared to the 1,153 normal participants, those with POAG tended to be older (P=0.003), male (P=0.003) and had a higher proportion of PVI (P=0.001) (Table 1).

By the end of April 2014 (median follow-up length: 9.38 years; range: 0.15-10.4), 306 (22.3%) of the 1,372 participants passed away, 294 (21.4%) did not return for re-examination because they declined participation (126) , relocated (122) or were uncontactable (41), leaving 777(56.6%) at the ten-year follow-up examination. Detailed follow-up information can be found in Figure 1. Those who passed away tended to be older (P<0.001), male (P<0.001), have a lower level of educational attainment (P=0.001), lower family income (P<0.001), higher proportion of PVI (P<0.001), larger VCDR (P<0.001) and be underweight (P=0.009). The medical history of hypertension and diabetes, CCT and mean IOP value were similar between the two groups (Table 2).

Among the 1153 participants without PACD or POAG, 235 (20.4%, 95%CI=18.1, 22.8%) passed away during the ten-year follow up period. The ten-year mortality rate of the 1153 participants was significantly lower than

those with PACS (43/136, 31.6%, 95%CI= 23.9, 40.1%), PAC (10/33, 30.3%, 95%CI= 15.6, 48.7%), PACG (10/21, 47.6%, 95%CI=25.7, 70.2%), and POAG (8/29, 27.6%, 95%CI= 12.7, 47.2%). The Kaplan-Meir survival estimates for types of glaucoma and mortality were displayed in Figure2. The age and gender adjusted cox proportional hazards model showed that the presence of PACG (HR=2.15, 95% CI=1.14, 4.04), PACD (HR=1.46, 95% CI=1.10, 1.95) and a VCDR of more than 0.3 (HR=1.53, 95% CI=1.16, 2.01) were significantly associated with a higher risk of mortality. No association was found between mortality and PACS, PAC, POAG and level of IOP. After adjusting for age, gender, education, income, history of diabetes and hypertension, BMI and PVI, the significant association between VCDR of more than 0.3 and poorer survival rate was still observed (HR=1.60, 95% CI=1.11, 2.33) (Table 3 and Table 4). A strong association between ten year mortality and a VCDR>0.5 (HR=1.37, 95% CI=1.06, 1.78) and VCDR≥0.7 (HR=1.62, 95% CI=1.18, 2.20) were found in the univariable analysis, whereas these associations disappeared after adjusting for confounders (all P>0.05, Supplement Table 1).

Discussion

In this population-based cohort study, we found a higher crude mortality rate among patients with POAG and any form of PACD (ranging from 7.2% to 27.2%). However, this difference was not replicated after multivariable confounders were adjusted for. Level of IOP was not significantly associated with an increased risk of ten-year mortality in the multivariable model, while VCDR of more than 0.3 was an independent predictor of long-term poor survival.

Controversy still exists around the association between POAG and the increased risk of mortality.[3-10, 12, 14-16, 18, 19] Almost 50 years ago, Egge et al found a decreased 30-year survival rate for patients with glaucoma in Norway. This finding was more pronounced among men using acetazolamide.[6] Results of the National Health Interview Survey (NHIS) 1986-1994 also supported the finding that glaucoma was related to an increased risk of all-cause and cardiovascular disease mortality among adults residing in the United States.[5] However, the glaucoma-mortality association in the NHIS is likely to have been impacted by recall bias (self-reported definition of glaucoma), misclassification error and underestimation of glaucoma cases. Furthermore, the diagnostic methods, definition and treatments of glaucoma have changed over the past five decades, making its findings less generalizable to today's glaucoma patients. More recent studies are in favor of the finding that POAG is not significantly associated with long-term survival.[3, 4,7-10, 12, 14-16, 18] The non-significant relationship in these studies are in agreement with the findings of our study. Differences in ethnicity, age distribution, study design, length of follow-up, definition of glaucoma, and confounding variables adjusted for in the multivariate model may explain the inconsistent results between studies. Alternatively, the small number of patients with POAG in the current study (n=29) may also explain the lack of association between POAG and ten-year mortality. However, a recent meta-analysis of observational studies[17] supported the finding of a non-significant relationship between POAG and risk of mortality.

Few studies have explored the relationship between different types of PACD and mortality. Similar to the current study, previously investigations have reported that the presence of PACD was not an independent risk factor for all-cause mortality.[7, 11, 13, 16] Thus far, only five-year data from the Beijing Eye

Study has reported that the presence of PACG was related to an increased risk of mortality using multivariate analysis.[3, 4] Interestingly, the ten-year data from the Beijing Eye Study found that mortality was not significantly associated with PACG.[16] Neither the Tanjong Pagar Study[11] or the Singapore Malay Eye Study (SiMES)[13] found significantly reduced survival among those with glaucoma. In the current study, we found that PACG was significantly associated with ten-year mortality in the age and gender adjusted model, but this significant association was not found in the multivariate model. This is likely due to other confounding factors not accounted for and the relatively small sample size.

The results of this study found a non-significant association between the level of IOP and ten-year mortality rate. Previous reports on the relationship between all-cause mortality and elevated IOP have been inconsistent.[7, 14, 18, 19] Excess all-cause mortality associated with ocular hypertension was found in the Barbados Eye Study and the Framingham Study,[18] while the APEDS[7] and a Swedish study[14] found no statistically significant association between elevated IOP and mortality risk. The APEDS was the only study to explore the association between VCDR and all-cause mortality. Consistent with the APEDS's finding that increasing VCDR was a predictor of ten-year mortality,[7] we also reported a significantly increased risk of mortality among participants with VCDR of more than 0.3. Considering that previous studies have indicated that global retinal nerve fiber layer decreased significantly with age and larger VCDR,[30, 31] one can speculate that the potential mechanism underlying the VCDR-mortality association may be caused by retinal nerve fiber layer thinning, a marker of ageing and frailty. Furthermore, the close relationship between neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease) and glaucoma, and the strong link between retinal nerve

fiber layer thinning and brain pathology adds weight to our speculation.[32-35] The non-significant association of other cut-offs, or linear of VCDR with all-cause mortality after adjusting for confounders might be due to the small sample size or non-linear relationship in our study. Alternatively, we can only speculate that VCDR of less than 0.3 (i.e., sufficient retinal nerve fibre layer) which represent physiological process of aging or neurodegeneration might be the threshold for better survival. Further studies with a larger study sample are needed to investigate the association between VCDR, retinal nerve fiber layer thickness and mortality.

Even though the mechanisms underlying the association between glaucoma/ocular hypertension-mortality is still unclear, it has been speculated that increased risk of mortality among patients with glaucoma or ocular hypertension might be caused by IOP-lowering treatment. Glaucoma-mortality association has been found to be more pronounced among men using acetazolamide.[6] The excess mortality linked to timolol maleate treatment for POAG found in the Barbados Eye Study[18] was also parallel to the hypothesis of this study. In the BMES, a dose-dependent pattern was observed in the association between duration of timolol maleate use and increased risk of cardiovascular disease mortality. In addition, previous studies verified the adverse effects of IOP-lowering treatments, including congestive heart failure, raised blood pressure and adverse respiratory effects.[36, 37] However, the dose-dependent pattern observed in the BMES may be due to detection bias. Approximately 50-90% of glaucoma patients remain undiagnosed.[7, 38] Participants in poorer health are more likely to access health care services and therefore have their glaucoma diagnosed and treated. The suggestion that detection bias is a cause of variable findings was further verified by the similar mortality rates between treated and untreated glaucoma patients in

multicenter randomized glaucoma treatment trials (Early Manifest Glaucoma Trial and Ocular Hypertension Treatment Study) and the observational Rotterdam study.[39-41] Even these two studies concluded that the use of glaucoma medications was associated with a reduced risk of mortality.[42, 43] Future investigations are required to assess this association further.

The strengths of the present study included the population-based study design, high participation rate, long-term follow-up, and standardized definition of glaucoma used. Of note, the present study was limited by the following points. Firstly, the small number of patients with glaucoma may explain the non-significant association between different types of glaucoma and mortality. Second, several important confounding factors, such as smoking status were not available in the present study. Nevertheless, the additional adjustment for these important confounding factors may further attenuate the magnitude of statistical significance and again verify the robustness of our results. Third, lack of data on the causes of death prevented the possibility of exploring the association between glaucoma and specific-cause mortality. Previous studies have reported a significant association between glaucoma and cardiovascular disease mortality.[5, 44] Fourthly, the fact that only participants with suspect glaucoma (VCDR of ≥0.7 in either eye (97.5th percentile of the Liwan Eye Study population), VCDR asymmetry ≥0.2 or IOP of ≥21 mm Hg) underwent VF assessment may underestimate the prevalence of glaucoma because participants with early glaucomatous changes may be missed. However, previous ocular history and IOP measurements were collected for each participant, possibly lowering the risk of underestimation. Fifthly, the relationship between changes in glaucoma related parameters and long-term survival were unavailable due to insufficient data and limited follow-up times. Finally, we did not collect information on utilization of IOP-lowering treatment.

Further studies are required to investigate the relationship between IOP-lowering treatment and long-term survival.

In conclusion, our findings suggest there is a higher level of crude mortality among patients with POAG, PACS or PAC. However, this difference was unable to be replicated after multivariable confounders were adjusted for. PACG was significantly associated with ten-year mortality in the age and gender adjusted model, but this significant association disappeared in the multivariable model. Level of IOP was not significantly associated with increased risk of ten-year mortality, while VCDR of more than 0.3 was an independent predictor of long-term survival. Further studies are needed to confirm these findings and to explore the association between different subtypes and treatments of glaucoma with long-term survival.

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Author Contributions: Study conception and design (LW, ZZ, MH); analysis and interpretation (LW, ZZ); writing of the article (LW, ZZ); critical revision of the article (WH, JS, MH); data collection (LW, ZZ, WH); administrative, technical or logistic support (JS, MH).

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Figure legend:

Figure1 Flow chart showing the enrollment and follow-ups of participants in the Liwan Eye Study

Figure2 Kaplan-Meier curve of PACS, PAC, PACG, POAG, all types of glaucoma, VCDR and mortality. A, PACS; B, PAC; C, PACG; D, POAG; E, PACG+POAG; F, VCDR.

Table 1 Baseline Characteristics of participants with POAG, PACG, PAC and PACS.

Basic characteristics	Normal, N (%)	PACD				POAG, N (%)
		PACS, N	PAC, N (%)	PACG, N	Total, N	
Total number (%)	1153(100)	136 (100)	33 (100)	21 (100)	190 (100)	29 (100)
Age (%)						
50-59	440 (38.2)	17 (12.5)	5 (15.2)	0 (0)	22 (11.6)	4 (13.8)
60-69	328 (28.5)	46 (33.8)	12 (36.4)	5 (23.8)	63 (33.2)	7 (24.1)
+70	385 (33.4)	73 (53.7)	16 (48.5)	16 (76.2)	105 (55.3)	18 (62.1)
Female (%)	639 (55.4)	95 (69.9)	26 (78.8)	13 (61.9)	134 (70.5)	8 (27.6)
No more than middle school	809 (79.3)	93 (79.5)	19 (63.3)	12 (70.6)	124 (75.6)	22 (78.6)
Income less than 1000RMB	585 (72.7)	78 (82.1)	22 (88.0)	12 (92.3)	112 (84.2)	19 (70.4)
BMI (kg/m^2)						
Normal (18.5-30.0)	716 (91.6)	79 (85.0)	16 (72.7)	11 (84.6)	106 (82.8)	23 (88.5)
Under weight (<18.5)	39 (4.99)	14 (15.1)	3 (13.6)	1 (7.69)	18 (14.1)	3 (11.5)
Over weight (≥30.0)	27 (3.45)	0 (0)	3 (13.6)	1 (7.69)	4 (3.13)	0 (0)
Hypertension (%)	416 (40.1)	61 (45.9)	15 (45.5)	10 (50.0)	86 (46.2)	16 (57.1)
Diabetes (%)	105 (10.1)	16 (12.0)	3 (9.09)	4 (20.0)	23 (12.4)	3 (10.7)

PVI (%)	228 (19.8)	45 (33.3)	12 (36.4)	10 (47.6)	67 (35.5)	13 (44.8)
CCT(μm)	541.7±33.2	535.5±33.4	542.9±29.8	550.4±26.9	538.4±32.5	542.5±35.2
IOP (mmHg, SD)	15.2±3.04	15.1±2.88	14.8±4.25	19.4±5.36	15.5±3.71	15.8±2.87

Abbreviations: PACD=Primary angle closure disease, POAC=Primary open angle glaucoma, PACG= Primary angle closure glaucoma, PAC= Primary angle closure, PACS= Primary angle closure suspect, BMI=Body mass index, PVI=Presenting visual impairment, CCT=central cornea thickness, IOP=Intraocular pressure

Table 2 Distribution of Basic Characters Associated with Mortality at Baseline Examination.

Basic Factors	Died, N (%)	Alive, N (%)	P-value
Total number (%)	306 (100)	1066 (100)	
Age (%)			<0.001
50-59	23 (7.52)	443 (41.6)	
60-69	66 (21.6)	332 (31.1)	
+70	217 (70.9)	291 (27.3)	
Female (%)	147 (48.0)	634 (59.5)	<0.001
No more than middle school	155 (67.7)	800 (81.4)	<0.001
Income less than 1000RMB	173 (83.2)	543 (71.7)	0.001
BMI (kg/m^2)			0.009
Normal (18.5-30.0)	169 (85.8)	676 (91.5)	
Under weight (<18.5)	22 (11.2)	38 (5.14)	
Over weight (≥30.0)	6 (3.05)	25 (3.38)	
Hypertension (%)	111 (44.4)	407 (40.6)	0.277
Diabetes (%)	33 (13.2)	98 (9.79)	0.120
PVI (%)	120 (39.5)	188 (17.6)	<0.001
VCDR(mean±SD)	0.49±0.18	0.44±0.17	<0.001
CCT(μm)	540.3±35.3	541.5±32.5	0.582
IOP (mmHg, SD)(mean±SD)	15.1±3.32	15.3±3.08	0.495

Abbreviations: PACD=Primary angle closure disease, POAC=Primary open angle glaucoma, PACG= Primary angle closure glaucoma, PAC= Primary angle closure, PACS= Primary angle closure suspect, BMI=Body mass index, PVI=Presenting visual impairment, VCDR= vertical cup-to-disc ratio，CCT=central cornea thickness, IOP=Intraocular pressure.

Table 3 Cox Proportional Hazards Models of ten-Year Mortality Categorized by Angle Status.

	Participants, N	Died, N	Mortality Rate, %(95%CI)	HR (95% CI)					
				Univariable	P-value	Age and Gender Adjusted	P-value	Multivariable Adjusted†	P-value
Angle Status									
Normal	1153	235	20.4 (18.1,22.8)	Reference [1]		Reference [1]		Reference [1]	
PAC	33	10	30.3 (15.6,48.7)	1.41(0.75,2.65)	0.284	1.27 (0.67,2.39)	0.463	0.85 (0.37,1.94)	0.702
PACS	136	43	31.6 (23.9,40.1)	1.59(1.15,2.19)	0.005	1.32 (0.95,1.83)	0.099	1.27 (0.84,1.90)	0.253
PACG	21	10	47.6 (25.7,70.2)	2.63(1.40,4.95)	0.003	2.15 (1.14,4.04)	0.018	1.60 (0.70,3.61)	0.263
PACD (PAC+PACS+PACG)	190	63	33.2 (26.5,40.3)	1.74(1.32,2.30)	<0.001	1.46 (1.10,1.95)	0.009	1.25 (0.87,1.79)	0.221
POAG	29	8	27.6 (12.7,47.2)	1.31(0.65,2.65)	0.449	0.74 (0.36,1.49)	0.395	0.70 (0.32,1.51)	0.359
Any glaucoma (PACG+POAG)	50	18	36.0 (22.9,50.8)	1.85(1.15,2.97)	0.012	1.18 (0.73,1.91)	0.505	0.96 (0.54,1.71)	0.877

Abbreviations: PAC= Primary angle closure, PACS= Primary angle closure suspect, PACG= Primary angle closure glaucoma, PACD=Primary angle closure disease, POAG=Primary open angle glaucoma, HR=Hazard ratio, CI=Confidence interval.

† Adjusted for age, gender, education, income, body mass index, presenting visual impairment, history of diabetes and hypertension.

Table 4 Cox Proportional Hazards Models of ten-Year Mortality Categorized by IOP and VCDR.

	Participants, N	Died, N	Mortality Rate, %(95%CI)	HR (95% CI)					
				Univariable	P-value	Age and Gender Adjusted	P-value	Multivariable Adjusted†	P-value
IOP									
Unit increase	-	-	-	1.02(0.99,1.05)	0.580	1.02 (0.99,1.05)	0.262	1.02 (0.99,1.05)	0.203
10~21	1267	272	21.5(19.2,23.8)	Reference [1]		Reference [1]		Reference [1]	
<10	43	12	27.9(15.3,43.7)	1.32(0.74,2.35)	0.349	1.16 (0.68,1.99)	0.680	0.91 (0.44,1.89)	0.798
>21mmHg	50	14	28.0(16.2,42.5)	1.34(0.78,2.28)	0.291	0.97 (0.48,1.97)	0.584	0.97 (0.49,1.91)	0.935
VCDR									
Unit increase	-	-	-	3.86(2.05,7.26)	<0.001	1.76 (0.94,3.30)	0.076	1.59 (0.74,3.46)	0.238
≤0.3	453	68	15.0(11.8,18.6)	Reference [1]		Reference [1]		Reference [1]	
>0.3	867	209	24.1(21.3,27.1)	1.71(1.30,2.25)	<0.001	1.53 (1.16,2.04)	0.002	1.60 (1.11,2.33)	0.011

Abbreviations: IOP=Intraocular pressure, VCDR=Vertical cup disc ration, HR= Hazard ratio, CI=confidence interval.

† Adjusted for age, gender, education, income, body mass index, presenting visual impairment, history of diabetes and hypertension.

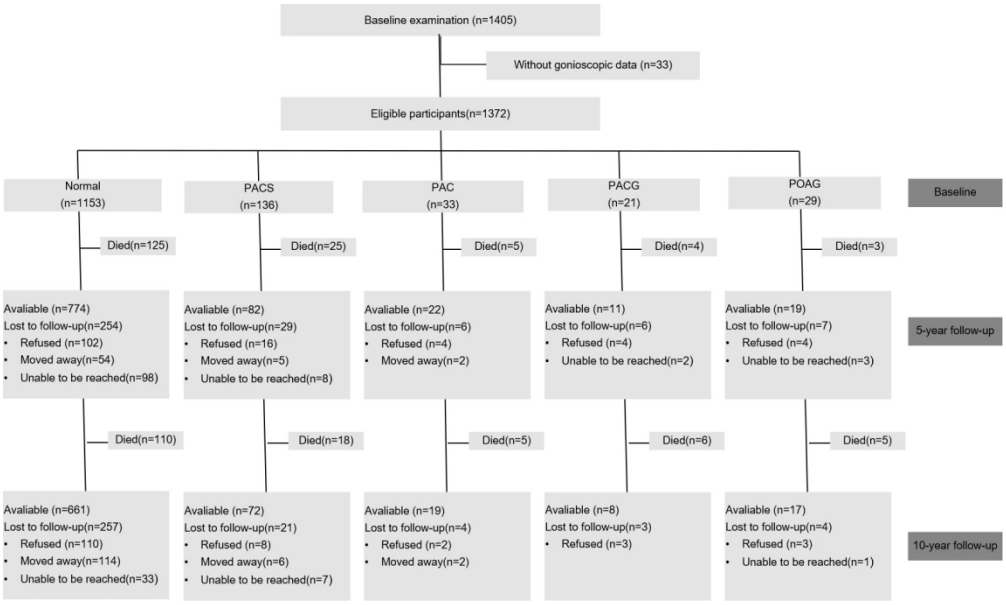

Figure1 Flow chart showing the enrollment and follow-ups of participants in the Liwan Eye Study

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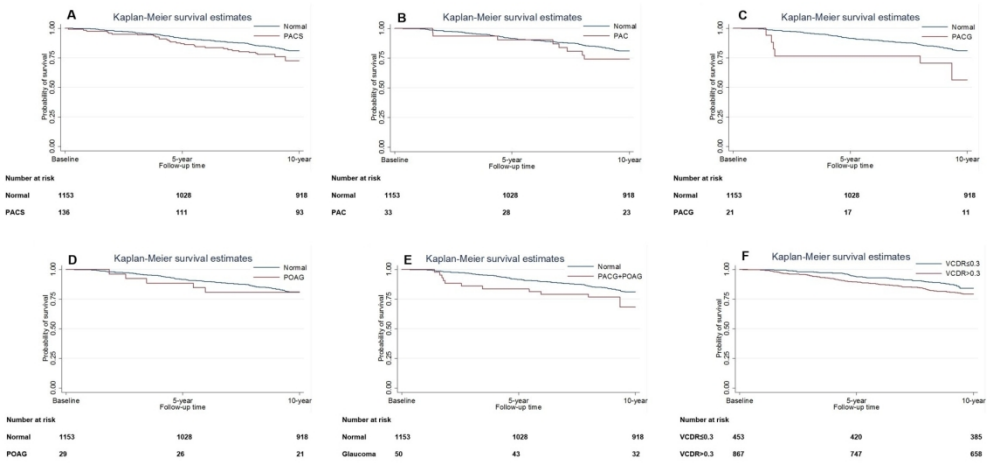

Figure2 Kaplan-Meier curve of PACS, PAC, PACG, POAG, all types of glaucoma, VCDR and mortality. A, PACS; B, PAC; C, PACG; D, POAG; E, PACG+POAG; F, VCDR

315x146mm (150 x 150 DPI)

Supplement Table 1 Cox Proportional Hazards Models of ten-Year Mortality Categorized by VCDR of different cut-off.

	Participants, N	Died, N	Mortality Rate, %(95%CI)	HR (95% CI)					
				Univariable	P-value	Age and Gender Adjusted	P-value	Multivariable Adjusted†	P-value
VCDR									
≤0.5	1012	197	19.5(17.1,22.0)	Reference [1]		Reference [1]		Reference [1]	
>0.5	308	80	26.0(21.2,31.2)	1.37(1.06,1.78)	0.016	1.10 (0.84,1.43)	0.500	1.11 (0.82,1.51)	0.490
VCDR									
<0.7	1160	229	19.7(17.5,22.2)	Reference [1]		Reference [1]		Reference [1]	
≥0.7	160	48	30.0(23.0,37.7)	1.62(1.18,2.20)	0.003	1.16 (0.84,1.59)	0.367	1.15 (0.80,1.67)	0.445

Abbreviations: IOP=Intraocular pressure, VCDR=Vertical cup disc ration, HR= Hazard ratio, CI=confidence interval.

† Adjusted for age, gender, education, income, body mass index, presenting visual impairment, history of diabetes and hypertension

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-9*
Bias	9	Describe any efforts to address potential sources of bias	7-9
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	10-11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.