British Journal of Ophthalmology

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Journal:	*British Journal of Ophthalmology*
Manuscript ID	bjophthalmol-2017-311654.R2
Article Type:	Global issues
Date Submitted by the Author:	n/a

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Keywords:	Epidemiology, Glaucoma

ORIGINAL RESEARCH

Glaucoma-associated long-term mortality in a rural cohort from India: The Andhra Pradesh Eye Disease Study

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Word count: 2, 496 (excluding title page, synopsis, abstract, reference and tables)

SYNOPSIS

This study on association of glaucoma and mortality found increasing cup:disc ratio as a risk factor for mortality, thus generating hypothesis about the association of loss of nerve fibre layer and mortality which needs exploration.

ABSTRACT

Aim: To evaluate glaucoma-associated mortality in a rural cohort from India.

Methods: The study cohort comprised individuals aged 40 years and above who took part in the Andhra Pradesh Eye Diseases Study (APEDS1) during 1996-2000. All participants underwent detailed comprehensive eye examination. Glaucoma was defined using International Society of Geographic and Epidemiologic Ophthalmology criteria. This cohort was followed up after a decade (June 2009-Jan 2010; APEDS2). Mortality hazard ratio (HR) analysis for ocular risk factors was performed using Cox proportional hazard regression after adjusting for socio-demographic, lifestyle and clinical variables.

Results: In APEDS1 2,790 individuals aged more than or equal to 40 years were examined. 47.4% were male. 45 participants had primary open angle glaucoma (POAG) and 66 had primary angle closure disease (PACD). Ten years later, 1, 879(67.3%) were available, 739(26.5%) have died and 172(6.2%) have migrated. While 22 of the 45(48.8%) with POAG and 22 of the 66(33.3%) with PACD have died.

In univariate analysis a higher mortality was associated with POAG (HR=1.9;95% CI: 1.23,2.94), pseudoexfoliation (HR=2.79;95% CI:2.0,3.89), myopia (HR=1.78;95% CI:1.54,2.06) and unit increase in cup:disc ratio (HR=4.49;95% CI:2.64,7.64). In multivariable analysis only cup:disc ratio remained independently associated with mortality (HR 2.5;95% CI:1.3,5.1). The association remained significant when other ocular parameters were included in the model (HR=2.1;95% CI:1.03,4.2).

Conclusions: This is the first longitudinal study to assessing association of glaucoma and mortality in a rural longitudinal cohort from India. Increased cup:disc ratio could be a potential marker for aging and would need further validation.

Key words: Glaucoma, Mortality, APEDS

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness and visual impairment (VI) globally.[1] The number of glaucoma cases worldwide was estimated to be 64.3 million in 2013, which is likely to increase to 76 million by the year 2020 and 111.8 million by 2040.[1] In India approximately 11.2 million adults above 40 years are estimated to have glaucoma: 6.5 million with primary open angle glaucoma (POAG) and 2.5 million with primary angle closure glaucoma (PACG).[2] Various studies have shown association of cataract and mortality.[3-7] However, the association between glaucoma and mortality is inconsistent with some studies reporting an association [8 9] while others have not.[10-16] Most of these studies were undertaken in Caucasian populations and most focused on POAG - only one study investigated a black population.[16] In the only study from Asia there was a strong association between mortality and primary angle closure glaucoma (PACG) but not with POAG.[17] Reports on the association of mortality with raised intraocular pressure (IOP) and pseudoexfoliation (PXF) are also inconsistent with some showing an association [10 16] whereas others have not.[12 18-20] In this study the association between mortality and all forms of glaucoma (POAG and primary angle closure disease), as well as IOP, PXF and cup:disc ratio (CDR) were investigated in a very well characterised population-based sample of adults recruited to the Andhra Pradesh Eye Disease Study (APEDS).

MATERIAL AND METHODS

Details of the methodology for APEDS, which was conducted between 1996 and 2000, are described elsewhere.[3] Data on mortality were obtained during an exercise undertaken between June 2009 and January 2010 the purpose of which was to identify as many participants as possible from the original APEDS, and recruit them for subsequent re-examination. For brevity, the original APEDS survey will be called APEDS1 and the present study will be referred to as APEDS2.

Detailed protocols for APEDS1 have been published.[21 22] In brief, standard examination included distance and near visual acuity (VA) at presentation (PVA) and best-corrected (BCVA) following refraction measured for each eye separately using logMAR (logarithm of minimum angle of resolution) charts. Detailed ocular examination included slit lamp biomicroscopy, intraocular pressure (IOP) measurement by Goldmann applanation tonometry, and gonioscopy with a NMR-K-2-mirror. Participants with suspicion of angle closure underwent laser iridotomy before dilated examination. Lens opacities were graded using the Lens Opacities Classification System (LOCS-III) and the Wilmer classification [23 24] after pupil dilation. Optic discs were evaluated using a 78 dioptre lens and the peripheral fundus was examined with a 20-D lens. Visual fields were assessed with automated Humphery Visual Fields (HVF) Analyser for those with any of the following features suggestive of glaucomatous disc damage: vertical CDR of 0.65 or more in either eye; asymmetry of CDR between eyes (>=0.2); notch; haemorrhage; rim <0.2 in any quadrant; nerve fibre layer defect; peri-papillary chorioretinal atrophy (alpha or beta); glaucomatous optic atrophy and non-glaucomatous optic atrophy. HVF was also performed if the IOP was $\geq$22mmHg in either eye or if there was a difference in IOP of $\geq$6mmHg between eyes. Visual field analysis was repeated if it was unreliable. Anderson's criteria were used to determine

glaucomatous visual field defects: a field defect that correlated with optic disc damage and met two of the three Anderson's criteria were considered to be significant.

Study definitions

These too have been described in our previous publication.[3 21 22] Blindness was defined as presenting visual acuity (PVA) less than 6/60 or central visual field less than 20° in the better eye [25]. Visual impairment was defined as PVA less than 6/18-6/60 or equivalent visual field loss [21]. The lens was examined after fully dilating the pupils. Because different types of cataract frequently co-exist, for analysis we considered pure nuclear, pure cortical, pure posterior subcapsular cataract (PSC) and mixed cataract. Those with total cataract were categorized as mixed cataract and those having undergone cataract surgery (unilateral / bilateral) formed a separate group. [26]. Age related macular degeneration (ARMD) was defined using the International Classification and Grading System [27] and diabetic retinopathy was defined using a modification of the standard classification system [28]. Glaucoma was defined using International Society of Geographic and Epidemiologic Ophthalmology (ISGEO) criteria.[29-31]

Hypertension was defined as a history of high blood pressure diagnosed by a physician and / or current treatment with antihypertensive medications and / or a blood pressure reading of ≥ 140/90 mm Hg. Diabetes was defined as a history of diabetes and / or taking diabetic medication and / or diabetic retinopathy was detected on clinical examination. The duration of diabetes since diagnosis was also documented. Body mass index (BMI) was calculated from the measured height and weight according to the formula weight (in kilograms) divided height (in meters) squared. World Health Organization categories of body mass index (BMI) were used i.e. underweight (BMI <18.5), normal (18.5 ≤ BMI < 25), over weight (25 ≤ BMI < 30), and obese (BMI ≥ 30).[32] For smoking, participants were categorized as never smoker, former smoker and current smoker. Current and former smokers were those who had smoked for a minimum of 1 year. Participants who had never smoked, or had smoked for less than 1 year were considered to be “never smokers”. [26]

Methods used in APEDS2

Extensive changes have taken place in the urban and semi-urban Hyderabad over the last decade, and the original urban area could not be delineated. Hence the tracing exercise, undertaken from 2009-2010, was limited to the three rural clusters. The purpose of tracing the original participants was as follows: to assess the mortality rate amongst those at APEDS1, and to determine factors at APEDS1 that predicted subsequent mortality e.g. lens status, VI, ARMD and glaucoma (POAG and angle closure disease), IOP, PXF and CDR, after adjusting for confounders.

The associations of mortality and visual impairment, lens status and ARMD have already been published.[3] The purpose of this study is to explore whether glaucoma (POAG and angle closure disease), IOP, PXF and CDR are associated with a different mortality risk.

During APEDS1 7,771/8,832 (88%) of those enumerated in 70 clusters were examined between 1996 and 2000; 2,790 (35.9%) were aged 40 years and above. Details of the tracing exercise and assessment of the cause of mortality have already been described.[3] In brief,

names and addresses of APEDS1 participants were extracted from the APEDS1 database. Field investigators visited each cluster to trace APEDS1 participants. A pilot study was undertaken to standardize data collection instruments. Following training, surviving participants who could be traced were interviewed. In households where APEDS1 participant(s) had died or migrated, a structured questionnaire was administered to the present household head to collect information on the cause and/or the reason of death and the year of death or migration, as applicable. Among those who died, time to death since the examination in APEDS1 was determined using date of examination in the database and reported year of death. In situations where the entire household had migrated, these questions were administered to neighbors. As formal death certificates were not available, the cause of death was based on verbal autopsy.

Ethics

The study was approved by the Institutional Review Board (IRB) of Hyderabad Eye Research Foundation, L V Prasad Eye Institute and adhered to the Tenets of the Declaration of Helsinki. As most participants were not literate, verbal consent was obtained after explaining the purpose of the study in presence of the village head of the village.

Data Analysis:

Data were analyzed using STATA 11.[33] For the continuous outcome variables (IOP and CDR), student's t test was used. For categorical data (ex, age group, gender, etc) Fisher's exact test was used. Cox-proportional hazard ratios were used to assess associations between mortality and glaucoma (POAG and angle closure disease), family history of glaucoma, IOP, CDR PXF, myopia and hyperopia.[34] Two models were used: in model 1 data were adjusted for age, gender, level of education, diabetes, hypertension, BMI and smoking status. In model 2, ocular variables likely to affect mortality risk (visual impairment, pure nuclear cataract, pure cortical cataract, pure posterior subscasular cataract, mixed cataract, history of cataract surgery and age related macular degeneration) were added to the model 1.[3] Tests of significance for survival curves were assessed using the log-rank test. Multi-colinearity between variables was assessed using variance inflation factors, and proportionality of the model was tested based on Schoenfeld residuals. Interactions for age and gender, age and CDR, and gender and CDR were assessed.

RESULTS

The interval between APEDS1 and APEDS2 ranged from 10-12 years (mean 11 years; SD: 0.81 year). Information was obtained on the status of all 2,790 individuals aged 40 years and above examined during APEDS1: 739 (26.5%) had died by APEDS2; 172 (6.2%) had migrated and 1,879 (67.4%) were still living in the area (i.e. they were "available"). 1322/2790 (47.4%) were male.

Migration was higher in females (52.3%), and was higher in one of the rural areas (Mahabubnagar, 9.1%). There was no significant difference in the mean age of those available in APEDS2 (mean 51.9 years; SD: 8.9 years) compared to those who had migrated (mean 52.7 years; SD: 10.9 years; P=0.34), but those who had died were significantly older at APEDS1 compared with those available or who had migrated (mean 62.3 years; SD: 10 years; P<0.001)(Table 1). Similarly, there were more deaths in males, illiterates, those with

hypertension and diabetes, current smokers and those with lower body mass index or overweight and obese (Table 1)

Table 1: Socio-demographic, lifestyle and systemic risk factors for mortality in participants available in APEDS2

Status at APEDS1	Risk Factors	Alive	Died	Total	
		n (%)	n (%)	n (%)	P value
Total		**2051 (73.5)**	**739 (26.5)**	**2790 (100)**	
Age group (years)	40 – 49	939 (91.3)	90 (8.7)	1029 (100)	
	50 -59	632 (80.3)	155 (19.7)	787 (100)	
	60 – 69	397 (55.5)	319 (44.5)	716 (100)	
	≥ 70	83 (32.2)	175 (67.8)	258 (100)	
					<0.001
Gender	Male	929 (70.3)	393 (29.7)	1322 (100)	
	Female	1122 (76.4)	346 (23.6)	1468 (100)	
					<0.001
Education	Illiterate	1327 (71.9)	518 (28.1)	1845 (100)	
	Class 1-5	450 (73.8)	160 (26.2)	610 (100)	
	Class 6-10	224 (83.9)	43 (16.1)	267 (100)	
	Class 11 and above	50 (73.5)	18 (26.5)	131 (100)	
					0.001
Hypertension	Absent	1224 (77.2)	362 (22.8)	1586 (100)	
	Present	827 (68.7)	377 (31.3)	1204 (100)	
					<0.001
Diabetes	Absent	2014 (74.1)	703 (25.9)	2717 (100)	
	Present	36 (50)	36 (50)	72 (100)	
					<0.001
Smoking status[$]	Never smoker	1648 (74.8)	554 (25.2)	2202 (100)	
	Former smoker	170 (80.2)	42 (19.8)	212 (100)	
	Current smoker	233 (62)	143 (38)	376 (100)	
					<0.001
Body Mass Index (BMI)	Normal	978 (78.2)	272 (21.8)	1250 (100)	
	Under weight	812 (71)	331 (29)	1143 (100)	
	Over weight	155 (75.2)	51 (24.8)	206 (100)	
	Obese	34 (70.8)	14 (29.2)	48 (100)	
					0.001
Alcohol consumption	Never Drinker	1371 (74.1)	480 (25.9)	1851 (100)	
	Former Drinker	500 (71.2)	202 (28.7)	702 (100)	
	Current Drinker	180 (76)	57 (25)	237 (100)	
					0.23

[$] Includes smoking cigarettes, Chuta (indigenous cigar) and Beedies (locally made cigarettes).

Table 2 shows the distribution of all forms of glaucoma, family history of glaucoma, PXF, myopia and hyperopia and other clinical traits among those available and those who had

died. There was a higher prevalence of POAG, PXF and myopia among participants who had died. Similarly, those died had a higher mean CDR (0.37, 95% CI 0.36,0.38) than those alive (0.34, 95% CI 0.33,0.35) and the difference was statistically significant P<0.001). However, there was no difference (p=0.43) in the mean IOP between those alive (15.2 mm of Hg, 95% CI 15.1, 15.3) and died (15.3 mm of Hg, 95% CI 15, 15.6).

Table 2: Distribution of glaucoma (POAG and angle closure disease), family history of glaucoma, PXF and myopia and hyperopia, by mortality status

Risk Factors	Alive	Died	Total	
	n (%)	n (%)	n (%)	P value
POAG				
Present	23 (51.1)	22 (48.9)	45 (100)	
Absent	2028 (73.9)	717 (26.1)	2745 (100)	
				0.001
PACG+PAC (NS)				
Present	18 (72)	7 (28)	25 (100)	
Absent	2033 (73.5)	732 (26.5)	2765 (100)	
				0.86
PACS (NS)				
Present	26 (63.4)	15 (36.6)	41 (100)	
Absent	2025 (73.7)	724 (26.3)	2749 (100)	
				0.14
Family history of glaucoma				
Present	3 (75)	1 (25)	4 (100)	
Absent	2048 (73.5)	738 (26.5)	2786 (100)	
				0.9
Pseudoexfoliation				
Present	24 (39.3)	37 (60.7)	61 (100)	
Absent	2027 (74.3)	702 (25.7)	2729 (100)	
				<0.001
Myopia				
Present	676 (64.6)	370 (35.4)	1046 (100)	
Absent	1374 (78.8)	369 (21.2)	1743 (100)	
				<0.001
Hyperopia (NS)				
Present	536 (76.6)	164 (23.4)	700 (100)	
Absent	1514 (72.5)	575 (27.5)	2089 ((100)	
				0.03

POAG: Primary Open Angle Glaucoma; PAC: Primary Angle Closure; PACG: Primary Angle Closure Glaucoma; PACS: Primary Angle Closure Suspect

Table 3 shows the univariable as well as multivariable analysis of ocular risk factors with mortality. In univariate analysis there was a higher hazard of mortality in those with POAG (1.9, 95% CI: 1.23-2.94), PXF (2.79, 95% CI: 2.0-3.89], myopia (1.78, 95% CI: 1.54-2.06) and for every unit increase in CDR (4.49, 95% CI: 2.64-7.64)(Table 3). A higher risk of mortality was not associated with family history of glaucoma, unit increase in IOP, hyperopia and PACD. In multivariable analysis mortality was higher with each unit increase in CDR i.e. the

mortality hazard increased by 2.5 (95% CI: 1.3, 5.1) in model 1, and by 2.1 (1.03, 4.2) in model 2 (Table 3). There was no association of mortality with POAG, PACD, family history of glaucoma, IOP, PXF, myopia or hyperopia. The association did not change when age was used as a continuous variable or with stepwise regression (data not shown). No interactions were observed between age and gender, age and CDR or gender and CDR (data not shown). Proportionality of the model was tested based on Schoenfeld residuals which showed a p-value of more than 0.05 (in models 1 and 2) suggesting that we accept proportional if hazards.

Table 3. Univariable and multivariable association of ocular factors with mortality in two different models

Ocular factors	Status	Univariable association	Multivariable association	Multivariable association
			Model 1[$] All glaucoma categories	**Model 2[^]** Glaucoma and other ocular pathologies
		HR (95% CI)	HR (95% CI)	HR (95% CI)
POAG	No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Yes	1,9 (1.23, 2.94)*	0.79 (0.45, 1.38)	0.82 (0.46, 1.44)
PACG+PAC	No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Yes	1.04 (0.5, 2.2)	1.38 (0.59, 3.25)	1.24 (0.5, 2.9)
PACS	No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Yes	1.55 (0.93, 2.59)	1.41 (0.8, 2.5)	1.33 (0.76, 2.3)
Family history of glaucoma	No			
	Yes	0.85 (0.12, 6.02)	0.78 (0.11, 5.57)	0.67 (0.1-4.8)
Unit increase in intraocular pressure		1.01 (0.99, 1.04)	0.99 (0.96, 1.02)	0.99 (0.96, 1.02)
Cup:disc ratio	Unit increase	4.49 (2.64, 7.64)*	2.5 (1.3, 5.1)*	2.1 (1.03, 4.2)*
Pseudoexfoliation	No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Yes	2.79 (2.0, 3.89)*	1.3 (0.92, 1.84)	1.22 (0.86, 1.73)
Myopia	No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Yes	1.78 (1.54, 2.06)*	1.12 (0.93, 1.35)	0.87 (0.71, 1.07)
Hyperopia	No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Yes	0.85 (0.71, 1.0)	1.03 (0.83, 1.27)	1.01 (0.81, 1.26)
Schoenfeld test[#]			0.2	0.07

[$]Adjusted for age, gender, education level, diabetes, hypertension, BMI and smoking status.
[^]Adjusted for age, gender, education level, diabetes, hypertension, BMI, smoking status, visual impairment, pure nuclear cataract, pure cortical cataract, pure posterior subcapsular cataract, mixed cataract, history of cataract surgery and age related macular degeneration.
POAG: Primary open angle glaucoma; PACG: Primary angle closure glaucoma; PAC: Primary angle closure; PACS: Primary angle closure suspect; [#]goodness-of fit test; Ref: Reference group; *: statistically significant (p<0.05)

After adjustment for age and gender, life table graphs of the probability of death by follow up time showed no association for POAG (HR=1.23; 95% CI: 0.8, 1.9), PAC and PACG (HR=1.06; 95% CI: 0.5, 2.25), PACS (HR=1.32; 95% CI: 0.8, 2.2) and PXF (HR=1.2; 95% CI: 0.84, 1.7). However, life table graphs of the adjusted probability of death with different baseline cup-disk ratios showed significant associations for three different cut-offs of cup-disk ratio i.e. 0.35:1 (HR=1.25; 95% CI: 1.1, 1.45), 0.5:1 (HR=1.27; 95% CI: 1.01, 1.6) and 0.7:1 (HR= HR=1.6; 95% CI: 1.2, 2.2). Figures 1-3 show life table graphs of the unadjusted probability of death by follow up time with three different baseline cup-disk ratios (0.35:1, 0.5:1 and 0.7:1).

DISCUSSION

There is conflicting evidence whether glaucoma is associated with mortality.[5 8 10 11 13 15-17] Most of the previous studies were on Caucasian populations and only included participants with POAG. Some of these studies demonstrated an association in univarable analysis, but this did not remain significant after adjusting for confounders.[5 10 11 13 15] The present study had similar findings for POAG. The United States National Health Interview Survey reported an association between glaucoma and mortality [8] but their definition of glaucoma was self reported and likely subject to enrolment bias. The variability across studies could be due to variation in study definitions, design, sample size, adjustment for confounders as well as the population or ethnic groups studied.

Some studies have reported an association between POAG and cardiovascular mortality, i.e., the Barbados study and the Blue Mountain Eye Study.[14 16] A meta-analysis supported an association with cardiovascular mortality but not for all causes of mortality.[10] In the present study it was not possible to collect reliable information on the cause of death and we were unable to explore this association.

Unlike Beijing Eye Study, we did not find an association between PAC and PACG with mortality.[17] This could be attributed to factors specific to the population or study design or the confounders adjusted in analysis as described above. As far as PXF was concerned, we found an association in univariable analysis but the association was not significant in multivariable analysis, as in other studies.[19 20]

The eye as a model of aging has been previously described.[35] We have also observed a consistent and significant association between vertical CDR and mortality which has not been described before. This finding raises the possibility that nerve fibre loss may be a marker of aging, particularly as it has been associated with neurodegenerative diseases such as Alzheimer's and Parkinson's disease.[36-38], and neuro-imaging abnormalities of the central nervous system (CNS) have been reported in patients with glaucoma.[39] Although glaucoma is undoubtedly a neurodegenerative condition of retinal ganglion cells, there is controversy concerning whether glaucoma is a primary neurodegenerative condition of the CNS or a primary optic neuropathy with secondary effects in the CNS.[36] Unfortunately, we did not measure nerve fibre layer thickness in the present study.

The major strengths of our study are that it was a population based sample with long-term follow-up and high participation rates, and a standard definition of glaucoma was used.

Limitations are lack of data on the causes of death and the possibility that the findings may be explained by unknown confounders. We also did not collect information on the use of anti-glaucoma medications. Apart from that, we did not measure disc size as cup-disc ratio is related to disc size as well as neuro-degeneration. Hence a structural association is also possible.

In conclusion, our data do not support an association between glaucoma and an increased risk of all-cause mortality. However, there was an association with increasing CDR. Based on our findings, after adjusting for disc size, the association between nerve fibre layer thickness and mortality is to be explored.

COMPETING INTEREST: No authors have any financial/conflicting interests to disclose.

FUNDING: Sightsavers International. The sponsor or funding agency has no role in design or conduct of this research

CONTRIBUTORSHIP STATEMENT

Rohit C Khanna (RCK): Contributions to the conception and design of the work, acquisition, analysis and interpretation of data. Drafting the work and revising it critically and final approval of the version published.

Gudlavalleti V S Murthy (GVSM): Contributions to the conception and design of the work and interpretation of data. Revising it critically and final approval of the version published.

Pyda Giridhar (PG): Contributions to acquisition of data. Revising it critically and final approval of the version published.

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Figure 1
Survival curves for cumulative proportion of mortality at cut off of cup-disc ratio of 0.35:1

Figure 2
Survival curves for cumulative proportion of mortality at cut off of cup-disc ratio of 0.5:1

Figure 3
Survival curves for cumulative proportion of mortality at cut off of cup-disc ratio of 0.7:1

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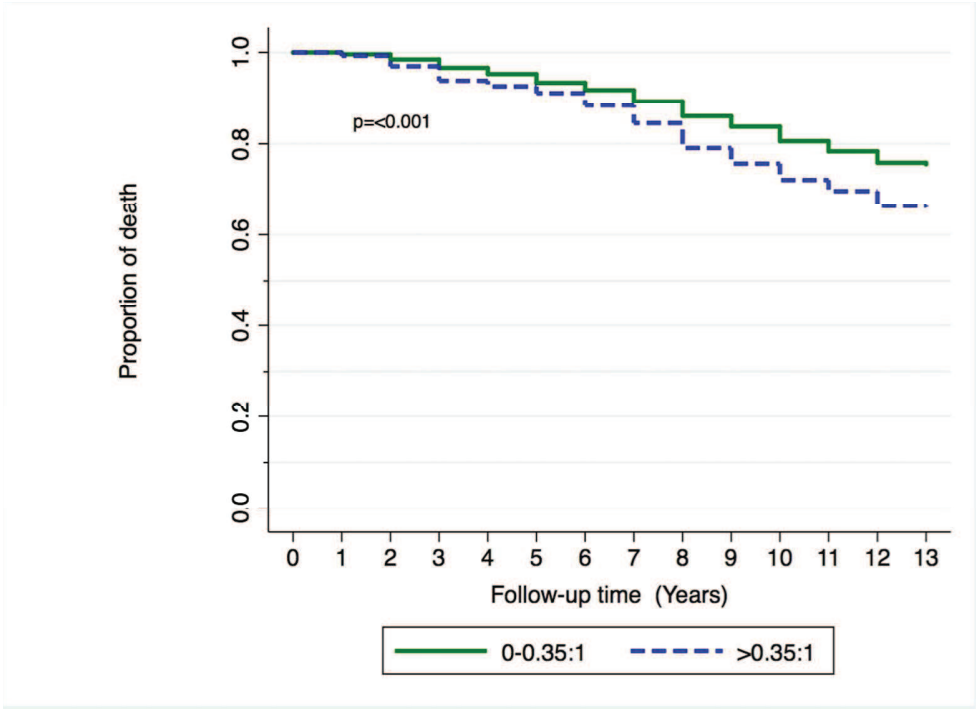

Survival curves for cumulative proportion of mortality at cut off of cup-disc ratio of 0.35:1

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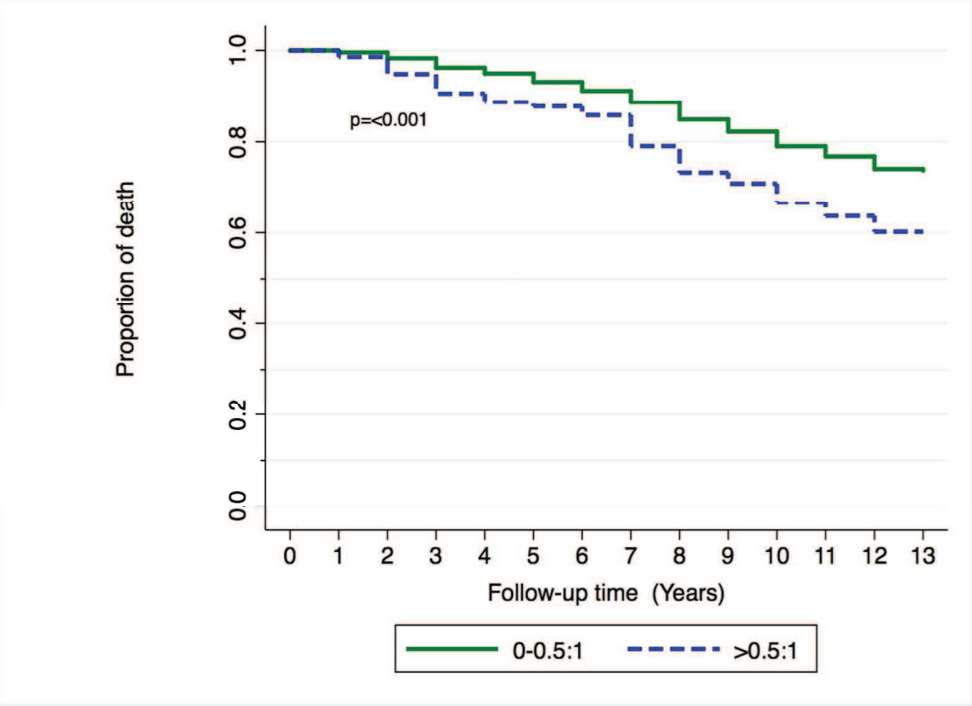

Survival curves for cumulative proportion of mortality at cut off of cup-disc ratio of 0.5:1

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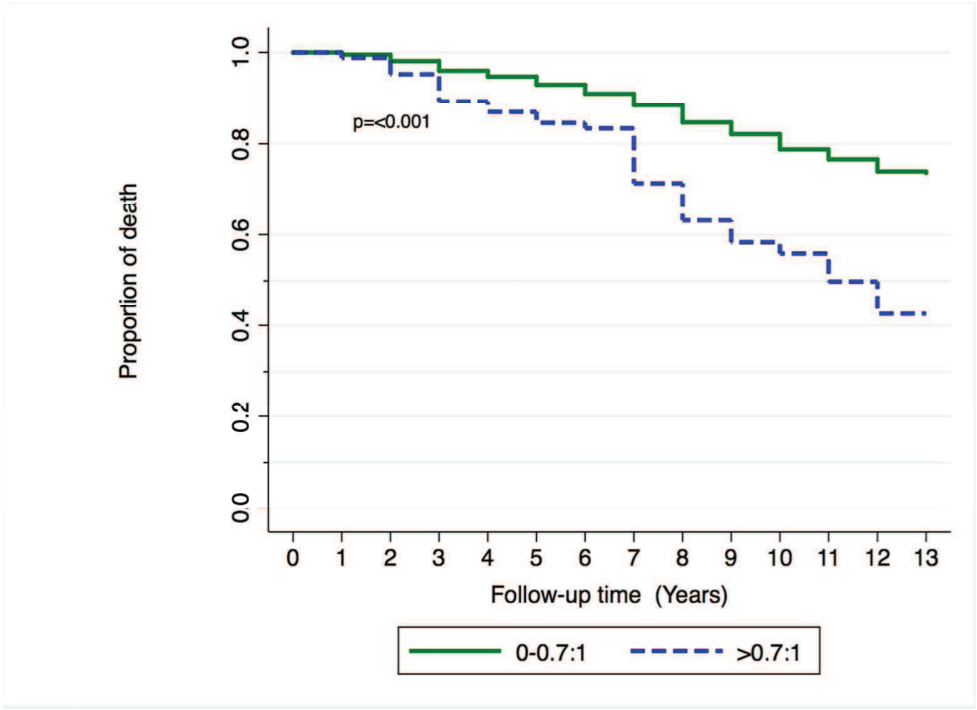

Survival curves for cumulative proportion of mortality at cut off of cup-disc ratio of 0.7:1

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