

1 **Determinants of Late Presentation of**
2 **Glaucoma in Hong Kong**

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22 **ABSTRACT**

23

24 **Background**

25

26 Glaucoma is the commonest cause of irreversible blindness
27 worldwide. As it is typically asymptomatic until advanced, the
28 risk of blindness from late presentation is higher than other eye
29 diseases. This study aims to investigate the risk factors for late
30 presentation of primary glaucoma patients.

31

32 **Methods**

33

34 We undertook a hospital-based case-control study of a random
35 sample of glaucoma patients from a hospital in Hong Kong.
36 Structured questionnaires and existing information from the
37 electronic patient record were used, and the odds of presenting
38 late were analysed by logistic regression.

39

40 **Results**

41

42 Of 210 recruited participants, 83 (39.5%) presented with
43 advanced glaucoma unilaterally or bilaterally. The mean age of
44 participants was 61.1±11.9 years, with 110 males (52.4%).

45 Univariate analysis revealed that male sex and primary angle-
46 closure glaucoma (PACG) have 3.06 (CI₉₅:1.71-5.48; P<0.001)
47 and 2.47 (CI₉₅:1.11-5.49;P=0.03) times higher odds of late
48 presentation, respectively. Multivariate analysis revealed late
49 presenters were 3.54 (CI₉₅:1.35-9.35; P=0.01) times more likely
50 to have PACG than primary open-angle glaucoma (POAG).
51 Patients with elevated baseline intraocular pressure (IOP) also
52 had 1.06 times higher odds of presenting with advanced
53 glaucoma (CI₉₅:1.02-1.11; P=0.002). Linear regression revealed
54 that PACG patients present with 7.12 mmHg higher IOP than
55 POAG patients (CI₉₅:4.23-10.0; P<0.001).

56

57 **Conclusion**

58

59 In conclusion, a high proportion of glaucoma patients present
60 late in Hong Kong, with gender and type of glaucoma being
61 significant determinants. Our study shows that PACG presents
62 with higher IOP and, along with male gender, are more likely to
63 have advanced disease than POAG.

64 INTRODUCTION

65

66 Glaucoma is defined as an optic neuropathy with a
67 characteristic pattern of visual field (VF) loss and structural
68 damage to the optic nerve(1). The clinical features of glaucoma
69 are related to the progressive loss of retinal nerve fibres,
70 manifesting as detectable changes to the optic nerve head, and
71 thinning of the peripapillary retinal nerve fibre layer, as well as
72 functional impairment such as VF loss or reduction in visual
73 acuity. There are multiple risk factors for glaucoma
74 development, including age(2), gender(3), and family history.
75 Currently, elevated intraocular pressure (IOP) is the only
76 modifiable risk factor(4).

77

78 Glaucoma blindness is the commonest cause of irreversible
79 blindness worldwide, and patients with visual impairment due
80 to glaucoma experience a significant drop in quality of life(5, 6).
81 In 2010, 6.5% of the global blindness was due to glaucoma. In
82 Hong Kong (HK), the prevalence of glaucoma is estimated to be
83 3.8% using data from the Guangzhou province(7), and
84 glaucoma contributes to 11% of all visual impairment(8). With
85 an ageing population worldwide, it is predicted that in 2040, the

86 number of patients affected by glaucoma globally will reach 112
87 million(6), with 81 million in Asia(9).

88

89 Late presentation has been shown to be a major risk factor for
90 glaucoma blindness in several studies(10-13). In Hong Kong (HK),
91 there are no existing data on the proportion of glaucoma
92 patients that present late but there is a general lack of public
93 knowledge about glaucoma(14). As a result, despite most of
94 the population in HK having ready access to high-quality eye
95 care services(15), referral to ophthalmologists may be delayed
96 until the glaucoma is advanced or end-stage. In addition, long
97 waiting times for public hospital appointments, high cost of
98 healthcare care in the private sector, and relatively low uptake
99 of private medical insurance, can all contribute to a delayed
100 diagnosis of glaucoma.

101

102 While primary open angle glaucoma (POAG) is around six times
103 more prevalent than primary angle closure glaucoma (PACG)
104 globally, PACG is more prevalent in some Asian populations(16).
105 Studies have suggested that PACG frequently presents with
106 higher IOP and more rapid VF loss, and thus more advanced
107 glaucoma, compared to POAG (17, 18). However, one study
108 reported that among Chinese, POAG presents with higher IOP
109 than PACG (19).

110

111 Studies have demonstrated that a positive family history of
112 glaucoma is associated with late presentation(20, 21). Genetic
113 predisposition may contribute to more advanced VF loss at
114 presentation due to a more aggressive disease subtype.
115 However, positive family history of glaucoma can also be
116 protective by enabling earlier presentation due to greater
117 awareness of symptoms. It has been previously reported that
118 patients with family history of glaucoma were three times less
119 likely to present late compared to those with no family
120 history(22). It would be interesting, therefore, to investigate
121 the effect of known first-degree family history on late
122 presentation in HK.

123

124 This study aims to measure the stage of disease for a cohort of
125 glaucoma patients who initially presented to the Lo Fong Shiu
126 Po (LFSP) Eye Centre, Grantham Hospital. This is a tertiary
127 referral and main clinical teaching centre for the Department of
128 Ophthalmology, University of Hong Kong. Potential factors for
129 late presentation, including mechanism of glaucoma, IOP level,
130 age, gender, family history, and socioeconomic status, are
131 analysed to determine if they have significant correlation with
132 late presentation.

133

134 There are 11 public hospitals and 8 private hospitals in HK that
135 provide ophthalmic services, as well as 96 private
136 ophthalmologists in private clinics, with the public sector
137 providing ophthalmic care for around 90% of patients in Hong
138 Kong(15, 23). Despite referral of glaucoma patients being based
139 on geographical proximity to hospitals, HK is a small region with
140 little variation of glaucoma prevalence between districts.
141 Therefore, the sample recruited in Grantham Hospital is likely
142 to be representative and generalisable to the entire city.

143

144 The prevalence of primary glaucoma in the HK population is also
145 comparable to nearby urbanized regions in Southeast Asia with
146 similar demographics and healthcare system, such as Singapore
147 (2.7%) [ref.(19)], Japan (3.0%) [ref.(24)], and Korea (1.1%)
148 [ref.(25)].

149 **MATERIALS AND METHODS**

150

151 The study was a hospital-based, case-control study carried out
152 at LFSP Eye Centre, Grantham Hospital, from May to June 2021.

153 This study was approved by the London School of Hygiene and
154 Tropical Medicine Ethics Committee and the Institutional
155 Review Board of the University of Hong Kong/Hospital
156 Authority Hong Kong West cluster (HKU / HA HKW IRB no. UW
157 21-376).

158

159 **Identification and recruitment of participants**

160

161 Primary glaucoma patients were identified retrospectively from
162 the hospital records and included as potential participants
163 according to the inclusion and exclusion criteria. They were
164 then put on a spreadsheet and randomly sampled to reduce
165 possibilities of investigator-induced selection bias, and
166 subsequently classified into case (late presentation of glaucoma)
167 or control by the mean deviation (MD) value, in decibels (dB),
168 on their VF at their first diagnosis. All patients recruited had
169 been initially diagnosed in our hospital, with their records
170 stored in the Electronic Patients Record (EPR). This allowed us

171 to classify patients into cases and controls by their VF at first
172 diagnosis.

173

174 **Inclusion and exclusion criteria**

175

176 Inclusion criteria:

177 1) Age 18 years or above

178 2) Diagnosed with either:

179 a. POAG (including normal tension glaucoma); or

180 b. PACG

181 on 1st January 2016 or later (but before study
182 recruitment date)

183

184 Exclusion criteria:

185 1) Secondary glaucoma

186 2) Other eye or neurological diseases that can affect VF, for

187 example: retinal detachment, corneal scarring,

188 moderate to severe cataract, other optic neuropathies

189 or neurological disorders affecting the visual pathway

190 3) Unable to give informed consent

191 4) Participants with unreliable VF, defined as fixation loss

192 $\geq 20\%$, false positive $\geq 10\%$, or false negative $\geq 10\%$.

193

194 **Case and control definition**

195

196 In this study, the MD value from a reliable automated threshold
197 VF test at, or soon after, glaucoma diagnosis was used as the
198 parameter for classification into either case or control(26). The
199 definition for severe visual glaucoma is referenced from the
200 LiGHT trial by Gazzard et al(27).

201

202 Cases were defined as severe glaucoma according to their level
203 of VF loss in the following criteria for the worse eye:

204 1) MD \leq -12 dB; or

205 2) Any point with sensitivity < 0 dB within central 5 degree;
206 or

207 3) Points with sensitivity < 15 dB within central 5 degree in
208 both hemifields (superior and inferior)

209

210 Controls were defined as mild or moderate glaucoma according
211 to the following VF criteria for the worse eye:

212 1) VF MD > -12 dB; or

213 2) At least 1 point that is < 15 dB within central 5 degree,
214 but none < 0 dB, and only 1 hemifield with central point
215 < 15 dB

216

217 Due to possible learning effect, results obtained from the first
218 VF may be unreliable. Therefore, if there was a second VF within

219 3 months of diagnosis, the MD of the second test was used as
220 the presenting VF instead.

221

222 EPR were obtained for cases and controls and the following
223 data recorded.

224

225 - Age

226 - Gender

227 - Type of glaucoma

228 - Cup-disc ratio

229 - Visual acuity

230 - VF indices (including MD)

231 - Baseline IOP at presentation (before treatment)

232 - Individual history of mild ocular diseases, for example,
233 mild cataract and its grading

234 - Residential address to identify housing standard

235

236 Chosen participants were contacted individually to obtain
237 informed consent to complete a standardized questionnaire on
238 their income, education, occupation. Recall of first-degree
239 family history of glaucoma, behavioural factors such as smoking
240 and drinking habits were also obtained from the questionnaire.

241

242 **Measuring social deprivation**

243

244 Due to the diversity between countries on the importance of
245 each dimension, it is difficult to form a unified guideline on the
246 measurement of deprivation level. It can be measured on
247 either district or individual levels. The Indices of Multiple
248 Deprivation (IMD) is a tool developed in the UK for the
249 measurement of social deprivation(28). The 3 most heavily
250 weighted domains (income, education, and occupation) were
251 chosen in this study as measurements of social deprivation in
252 HK, while housing is also included for analysis since there is a
253 large gap observed in living environment between those that
254 are deprived and their counterparts. These dimensions will be
255 compared between the case and control group for possible
256 association between social deprivation and glaucoma severity
257 at diagnosis.

258

259 Income level of the individual is divided into 4 categories by
260 their monthly household income (in HK dollars): \$0-10000,
261 \$10001-25000, \$25001-50000, and \$50001 or above. Education
262 is classified into 3 levels by the ISCED 2011(29), while
263 participants' occupations are classified into low (skill level 1),
264 medium (skill level 2), and high (skill levels 3-4) by the ISCO-
265 08(30). Housing is classified into public and non-public.

266

267 **Statistical analysis**

268

269 There are no relevant data to inform an estimate of the
270 expected difference in rates of late presentation between those
271 of different levels of deprivation in HK. A previous UK study has
272 shown that socioeconomically deprived patients had
273 approximately 3 times the risk of late presentation(22), and this
274 seems a clinically important difference hence was selected for
275 the power calculation. We calculated that at least 48 cases and
276 95 controls are required to detect a threefold increase in odds
277 of late presentation in a factor among 20% of control at a power
278 of 80% and significance level at 5%.

279

280 Analysis was completed on STATA/SE 16.1. The odds of late
281 presentation were analyzed by univariate and multivariate
282 logistic regression on 3 models to estimate the significance of
283 observed differences between case and control. Central
284 tendency measures were performed on descriptive statistics for
285 analysis.

286 RESULTS

287

288 There were 210 participants, among which 83 (39.5%)
289 presented with advanced glaucoma in at least one eye. **Table 1**
290 summarizes the demographics, socioeconomic, and medical
291 characteristics of recruited participants with respect to their
292 case-control status. The mean age was 61.10 ± 11.88 (mean \pm
293 SD), with 110 males (52.4%) and 100 females (47.6%). More
294 than 60% were unemployed/retired and economically
295 dependent. Most were POAG (86.2%).

296

297 Univariate analysis

298

299 **Table 2** summarised the findings of univariate analysis of each
300 study factor. Males ($P < 0.001$), PACG ($P = 0.03$), and higher IOP
301 ($P = 0.001$) had significantly greater odds of late presentation.

302

303 Multivariate models

304

305 To determine if our study factors were independently
306 correlated with the odds of late presentation, the odds ratios
307 (ORs) were adjusted by 3 multivariate models, summarised in
308 **Table 3**. Model I, II, and III adjusted for age; age and gender; or

309 age, gender, behavioral and cognitive factors, respectively,
310 which can facilitate to demonstrate the possible effect of
311 aggressive diseases(31).

312

313 In model I, adjustment by age alone had negligible effects on
314 the ORs of all study factors except for high education level,
315 which had lower odds after adjustment. In model II, additional
316 adjustment for gender showed lower odds for participants
317 living in non-public housing. Participants with PACG had
318 increased odds in model II and III when compared to unadjusted
319 model and model I. There was weak evidence of higher odds for
320 participants in the low skilled occupation group (group I) to
321 present late in model III (P=0.06), but not in model I and II.
322 Multivariate analysis on IOP (left, right and worse eye) showed
323 that higher baseline pressures were associated with increasing
324 risk of late presentation in all 3 models.

325

326 PACG and high baseline IOP both increased the odds of
327 presenting with advanced glaucoma (late presentation).

328 Subsequent two-sample independent t-test confirm mean
329 baseline IOP in PACG is significantly higher than in POAG
330 (P<0.001). Both univariate and multivariate linear regression
331 by these models showed a significantly higher presenting
332 (baseline) IOP in PACG than POAG (P<0.001) [Table 4]. This

333 hinted at a possible causal relationship in which PACG patients
334 have higher IOP and thus faster progression of glaucoma in
335 diagnosis.

336 **DISCUSSION**

337

338 Almost 40% of our randomly selected participants presented
339 with advanced glaucoma based on perimetric mean deviation
340 criteria, which was surprisingly high considering that Hong Kong
341 has a well-developed and easily accessible public health system.
342 However, this is comparable to previous studies from regions
343 with similar level of healthcare, such as Canada (47.9%)(12) and
344 Sweden (42.2%)(13). Both males and PACG patients were more
345 likely to present with advanced glaucoma in our study.

346

347 Although not statistically significant from univariate analysis,
348 the odds of late presentation according to age appear to show
349 a U-shaped trend with those <40 two to four times the risk
350 compared to 41-50 (P=0.06), 51-60 (P=0.10) and 61-70 (P=0.10)
351 **[Figure 1]**; while the risk appears to increase slightly again for
352 >80. Since glaucoma is more common above age 50, patients
353 presenting below age 40 may either have a more rapidly
354 progressive form of the disease or are more reluctant to seek
355 early assessment, which could be due to lower incidence of
356 major eye disorders in younger people, or greater
357 inconvenience in scheduling consultations in working age adults

358 (especially in the HK's public sector where there's less flexibility
359 in appointment booking).

360

361 In this study, there is very strong evidence that male gender
362 ($P < 0.001$) is a significant risk factor. This is consistent with other
363 studies reporting male gender as a risk factor associated with
364 late presentation(22, 31, 32). Although both genders have
365 ready access to public healthcare in HK, it is likely that most men
366 are the main household income earner and the inconvenience
367 of arranging for an ophthalmic assessment, especially in the
368 public health sector, may explain their higher risk for late
369 presentation. This is particularly relevant in our study, as most
370 of participants are still working with a mean age of 61.

371

372 PACG and elevated IOP were identified as significant risk factors
373 for late presentation, while both univariate and multivariate
374 linear regression have demonstrated strong evidence that
375 PACG presents with higher IOP. This result is comparable to
376 those from other studies showing PACG patients have higher
377 IOP, which is a significant risk factor for glaucoma progression,
378 and therefore more likely to present with more advanced
379 disease(17, 18).

380

381 Previous studies from different regions have suggested social
382 deprivation as a risk factor for late presentation of multiple
383 chronic diseases, including glaucoma(12, 21, 22, 32-34). This
384 finding is not confined to low-and-middle-income regions but
385 include high-income ones too. In contrast, our current study did
386 not find any significant relationship between socioeconomic
387 status of an individual and their late presentation of glaucoma
388 in univariate or multivariate analysis. There was weak evidence
389 in univariate analysis (P=0.10) and multivariate analysis Model
390 III (P=0.07) of possibly higher risk in the low-skilled occupation
391 group, but a larger sample size may be required to confirm this.
392 As participants in lower skilled occupations often have longer
393 working hours (for example, security guard) and, as for younger
394 and male participants, may have greater difficulty in scheduling
395 healthcare consultations.

396

397 Interestingly, a first-degree family history of glaucoma
398 conferred no significant reduction to the odds of late
399 presentation. A possible reason may be a lack of awareness that
400 primary glaucoma may present with genetic clustering. Further
401 research on glaucoma knowledge and awareness of patients
402 would help to confirm this hypothesis.

403

404 **Healthcare implications**

405

406 Almost 40% of our glaucoma patients presented late, possibly
407 due to the lack of any glaucoma screening programme and low
408 disease awareness. While a population-wide screening
409 programme for glaucoma specifically may not be cost-
410 effective(35), recent advancements in artificial intelligence and
411 machine learning may have, or will likely, change this situation,
412 especially when combined with screening for other common
413 and treatable eye conditions (age-related or myopia-related
414 macular degenerations) in high risk populations (age >50, family
415 history, high myopia)(36).

416

417 The possible barriers to early glaucoma diagnosis in the public
418 sector faced by certain population groups in HK, such as age <40,
419 men, and those in low-skilled occupations. A possible common
420 factor among these groups appears to be scheduling of
421 ophthalmic assessment at a convenient time and place. Our
422 current study was not designed to explore this issue, but future
423 studies looking into the role of working culture (including
424 normal working hours and ease of obtaining medical leave) for
425 different occupations would be warranted. Here again,
426 advancement in telemedicine will likely improve access to
427 ophthalmic care and mitigate this problem in the future(37).

428

429 There are some possible weaknesses of our study. This includes
430 recall bias, as the social deprivation status relies on the
431 participants' recollection of the period when they were first
432 diagnosed with glaucoma. This may be difficult or inaccurate if
433 this had occurred many years ago. However, we believe our
434 results should not have been significantly affected, as social
435 deprivation status tends to be stable over short periods of time
436 and we had intentionally only recruited participants diagnosed
437 with glaucoma within 5 years of the study.

438

439 Another limitation lies in the scope of the study. Data collection
440 was confined to a single hospital, out of 11 public hospitals
441 providing ophthalmic service in HK, and no participants using
442 private medical services were included. However, we do not
443 believe there would be a significant difference between public
444 hospital patients from different regions of HK, given the small
445 geographic area of this city (1,106 km²). Since around 90% of
446 patients in HK are under the care of public health services, we
447 believe our results is generalizable to the majority of glaucoma
448 patients in this city.

449

450 In conclusion, this study has highlighted the high proportion of
451 glaucoma patients who present with advanced disease in Hong
452 Kong. Male gender and PACG were significant risk factors for

453 late presentation, while age <40 and low-skilled occupation
454 may also be possible risk factors that warrants further
455 exploration with a larger sample size. Our study also confirms
456 that PACG presents with higher baseline IOP, as previously
457 reported, which may explain their more advanced disease on
458 presentation.

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460

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463

464 **CONFLICT OF INTEREST**

465

466 The authors declare no conflicts of interest.

467

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469

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471

472 **AUTHOR CONTRIBUTIONS**

473

474 A.C.K.L. was responsible for the development of the
475 methodology, data analysis method, and the drafting of the
476 article under the supervision of J.C.C., J.C.B, and W.N., J.C.C.,
477 J.C.B and W.N. advised on the development of the methodology,
478 interpretation of the findings and drafting of the manuscript. All
479 authors have read and approved the final manuscript.

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617 **TITLES AND LEGENDS TO FIGURES**

618 **No table of figures entries found.** Table 1 – Participants’
619 demographics, socioeconomic and medical characteristics
620 Table 2- Univariate analysis of case-control status to study
621 factors
622 Table 3- Odds ratio after adjustment by the 3 multivariate
623 analysis models
624 Table 4- Two-sample t-test, univariate, and multivariate
625 analysis of IOP in the worse eye between POAG and PACG
626 Figure 1- Odds ratio and 95% CI of late presentation against
627 age distribution

628

629 **DATA SHARING**

630

631 Deidentified individual participant data that underlies the
632 results reported in this article are available for sharing. Data will
633 be available upon request immediately following publication
634 and ending 5 years following article publication, with
635 investigators whose proposed use of the data has been
636 approved by an independent review committee identified for
637 this purpose. Proposals should be directed to
638 laianakinlai2@gmail.com.

639

640 **ETHICAL APPROVAL**

641

642 This study was approved by the London School of Hygiene and

643 Tropical Medicine Ethics Committee and the Institutional

644 Review Board of the University of Hong Kong/Hospital

645 Authority Hong Kong West Cluster.