A prospective study on effectiveness of elevated intraocular pressure as a criterion for glaucoma referrals by optometric practitioners in Sweden

Karin Landgren[1] and Dorothea Peters[1,2]

[1]Department of Ophthalmology, Skåne University Hospital, Malmö-Lund, Sweden
[2]Department of Clinical Sciences in Malmö, Ophthalmology, Lund University, Malmö, Sweden

ABSTRACT.

Purpose: To evaluate the outcome of referrals for suspected glaucoma based on elevated intraocular pressure (IOP) made by optometric practitioners in Sweden.
Methods: This prospective study included 95 individuals referred to the Skåne University Hospital Malmö, Sweden, during 2019, by optometric practitioners, based on elevated IOP. Positive outcome was defined as a diagnosis of glaucoma, or a diagnosis of suspected glaucoma. Referral accuracy was analysed. Positive predictive values (PPV) of different hypothetical IOP and age thresholds were calculated.
Results: In 34% (95% CI: 24–43%) of the referrals, no eye disease was found. Intraocular pressure (IOP) was the only referral criterion in 77% (73/95). The PPV was 35% (95% CI: 25–45%) for all referrals, 27% (95% CI: 16–38%) for IOP-only referrals and 59% (95% CI: 36–82%) for referrals including additional findings. In IOP-only referrals, no definite diagnosis of glaucoma was made in any patients <45 years of age. Applying a theoretical age limit of ≥45 years with a hypothetical IOP limit of ≥25 mmHg in patients 45–69 years and of ≥22 mmHg in patients ≥70 years increased the PPV to 42% (95% CI: 27–57%). IOP-only referrals would have been reduced by 27% without missing any glaucoma cases.
Conclusion: The overall predictive value of the referrals was poor. Glaucoma resources would have been used more effectively by increasing the required age for IOP-only referrals to ≥45 years in combination with different IOP thresholds for certain age groups.

Key words: effectiveness – IOP – open-angle glaucoma – optometric practitioners – referrals

Introduction

It has been estimated that approximately 76 million people are currently affected by glaucoma worldwide (Tham et al. 2014). Nevertheless, according to several population-based studies, only 50% or fewer of all individuals with glaucoma are aware of their condition (Topouzis et al. 2008; Karvonen et al. 2019; McCann et al. 2020). At the same time, many patients are over-diagnosed and over-treated (Founti et al. 2018a). As glaucoma is associated with advancing age, the demand on the glaucoma health care can be expected to increase in the future together with increasing life expectancy (Rudnicka et al. 2006; Tham et al. 2014; Chan et al. 2017).

Simulation models of screening for glaucoma have not been found cost-effective and show variable results (Burr et al. 2007; Vaahtoranta-Lehtonen et al. 2007). Instead, glaucoma suspects are usually detected through opportunistic case finding by eye care professionals, for example opticians or optometrists (Bowling et al. 2005), or found by general practitioners or ophthalmologists when consulted for other eye-related symptoms.

The high number of false positive glaucoma referrals made by optometric practitioners (i.e. opticians and optometrists) has previously been identified as a problem (Bowling et al. 2005). Various glaucoma referral refinement strategies have been evaluated, mainly in the UK (Parkins & Edgar 2011; de Vries et al. 2012; Ratnarajan et al. 2013; Keenan et al. 2015; Ratnarajan et al. 2015; Sii et al. 2019). Nevertheless, poor accuracy, with many false positive referrals, was still found in a recent study by Founti and co-workers (Founti et al. 2018b), who investigated the outcome of glaucoma referrals in four, non-Scandinavian, European countries, and in the UK. Conducting medical examinations on healthy people may not only expose them to unnecessary psychological stress (Davey et al. 2013), but the unnecessary use of resources will also place

extra demands on healthcare services to glaucoma patients.

In Sweden, most primary glaucoma referrals to ophthalmology departments are made by optometric practitioners. An elevated intraocular pressure (IOP) is a commonly accepted criterion for glaucoma referral. However, there is no consensus regarding the threshold for IOP, nor whether additional examinations should be carried out prior to referral. Pseudoexfoliation (PEX) and pseudoexfoliation glaucoma (PEXG) are common in some Scandinavian countries including Sweden (Ekstrom 1996; Astrom et al. 2007; Ekström & Winblad von Walter 2020), and PEX should therefore be taken into consideration when developing referral strategies in these countries.

The aim of the present study was to improve our knowledge on the outcome of referrals for glaucoma based on elevated IOP by optometric practitioners in a Swedish setting. We hope that the results may help in developing better guidelines for glaucoma referrals applicable in Sweden and in other countries with a similar prevalence of PEXG.

Subjects and Methods

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Review Board of Lund University, Sweden. All subjects received written and oral information before inclusion, and provided their written informed consent.

All referrals received by the Department of Ophthalmology, University Hospital of Skåne, in Malmö, after approval of the study (17 January 2019) until the end of December 2019, from optometric practitioners, concerning suspicion of glaucoma was consecutively evaluated for eligibility to participate in this study. Only subjects aged 18 years or older, with an IOP of at least 21 mmHg in at least one eye, were eligible. Subjects with self-referrals were eligible when the initial reason for referral was a high IOP measured by an optometric practitioner. Subjects with an IOP < 21 mmHg, but also a central corneal thickness (CCT) measured by the referring optometric practitioner leading to a corrected IOP of at least 21 mmHg (according to the referring optometric practitioner) were also included. Referrals concerning patients presenting with symptoms of acute angle closure or already under treatment for glaucoma or ocular hypertension (OHT) were not eligible for inclusion in this study. However, individuals previously treated for high IOP, but no longer being treated for this and not being monitored by an ophthalmologist were included.

All visits at the Department of Ophthalmology followed a standardized examination protocol, and a case report form was used for all data collection, including information from the referrals. The first part of each examination was performed by an optometrist (K.L.), that is measurement of IOP, visual field (VF), optic nerve head (ONH) and CCT. A slit lamp examination of the eye and a second IOP measurement after pupil dilation were then carried out by an ophthalmologist specialized in glaucoma (D.P.). In order to minimize observer bias, the optometrist had not seen the referral, nor the patient's medical records before the examination. The ophthalmologist did not have access to the results from the optometrist's examination until after all examinations were performed. Also, the participants were encouraged to, and succeeded in, not revealing any relevant information to the examiners before the measurements and assessments had been completed.

The study protocol included automated refraction and visual acuity measurements with an Auto Kerato-Refractometer (KR-800S; Topcon, Tokyo, Japan). The IOP was measured before and after dilatation with Goldmann Applanation Tonometry (GAT). Standard automated VF examination was performed with a Humphrey perimeter (Carl Zeiss Meditec, Dublin, CA, USA) using the 24-2 Swedish interactive thresholding algorithm (SITA) with the SITA standard programme. Visual field (VF) results were defined as reliable if a clear blind spot could be seen on the VF printout and the false positive response rate was below 15%. In cases where the results of perimetry were not reliable, as described above, or there were clinical signs of poor participation, the subject was invited for a second visit at which the VF test was repeated.

Following the current Swedish clinical guidelines for glaucoma practice (Heijl et al. 2012), anterior chamber angles were assessed according to Van Herick et al. (1969) (Dabasia et al. 2015) and a gonioscopy examination was only performed if considered necessary. Ultrasonic pachymetry (Pachette pachymeter, model DGH-500, SN-3060; D GH Technology Inc., Exton, PA, USA) was performed five times in each eye and the average was calculated. In subjects with unstable fixation, due to excessive blinking reflexes or nystagmus, pachymetry was performed more than five times until reliable results were obtained. Mean CCT values were used to calculate adjusted IOP values using the Ehlers correction factor (Ehlers et al. 1975) in patients with normal VFs and normal ONH appearance and an uncorrected IOP between 22 and 27 mmHg in order to differentiate between 'OHT' or 'no ocular pathology'. Pupils were dilated with 0.5% tropicamide and 2.5% phenylephrine. At least 10 min after administration, the ONH was assessed with optical coherence tomography (OCT) using a spectral domain Cirrus HD-OCT version 7.0.1.290 (Carl Zeiss Meditec, Dublin, CA, USA) and a 35° digital fundus camera. An OCT signal strength of at least 7 was required.

The ophthalmologist performed a slit lamp examination in dilated eyes. The presence of PEX and pigment dispersion syndrome was determined and the lens was assessed either as clear, cataract or pseudophacic. The appearance of the ONH was evaluated using the findings in biomicroscopy. The cup shape and depth, as well as the neuroretinal rim, were evaluated in relation to the disc size and shape. For example, a notch in the ONH was considered structural glaucomatous damage, but a large cupping alone was not. Optical coherence tomography (OCT) findings [e.g. retinal nerve fibre layer (RNFL) defects] were interpreted taking potential software errors and imaging artefacts into account. The presence of structural glaucomatous damage was determined clinically by combining the results of the examinations described above. All patients in need of treatment or further follow-up were transferred to the ordinary healthcare system at our hospital.

Following examination, each eye was categorized individually according to the following definitions.

- **Glaucoma**, repeatable glaucomatous VF defect (VFD) in the same area of the field with the Glaucoma Hemifield Test (GHT) 'outside normal limits' in at least one test, and either 'outside normal limits' or 'borderline' in the other test, or one VF measurement with glaucomatous VFD with GHT 'outside normal limits' confirmed by corresponding ONH appearance with structural glaucomatous change in the disc and/or the RNFL, assessed clinically by biomicroscopy and OCT (i.e. open-angle glaucoma, with or without PEX or pigment dispersion syndrome).
- **Suspected glaucoma,** further follow-up required for definitive diagnosis.
- **Ocular hypertension (OHT)**, normal VF, normal ONH and an IOP of ≥22 mmHg (adjusted for CCT according to the Ehlers correction factor in cases with uncorrected IOP between 22 and 27 mmHg).
- **Other ocular pathology**: including other reasons for VF loss.
- **No eye disease:** neither treatment nor further monitoring required.

The first two categories were defined as positive outcomes of glaucoma referral, and the other three as negative outcomes. Patients diagnosed as having glaucoma were divided into three glaucoma stages (early defect: ≤−6.00 dB; moderate defect: −6.01 to −12.00 dB and advanced defect ≥12.01 dB) according to the Mean Deviation (MD) in decibel (dB) in the worse eye (Mills et al. 2006).

Referrals were defined as IOP-only when initiated based on an elevated IOP-only and as IOP-plus when including at least one additional finding from the assessment of the ONH and/or assessment of VF. In the IOP-only group, data were collected on whether the IOP was measured more than once, or whether an IOP measurement was accompanied by a CCT measurement. In the IOP-plus group, the descriptions of VF and ONH in referrals were defined as normal if not clearly described as suspicious for glaucoma. Fundus photographs of the ONH or VF printouts included in the referral, but not evaluated in any way by the optometric

practitioner were defined as 'not assessed before referral'.

Elevated IOP was defined as ≥22 mmHg and an IOP of ≤21 mmHg was defined as normal IOP using the measurements at the clinical visit. Only uncorrected IOP values were used for the comparisons between IOP values measured by the optometric practitioner prior to referral and the IOP measured at the clinical visit.

Positive predictive value (PPV) was calculated for all participants, and for the group with IOP-only referrals and the group with IOP-plus referrals. In the IOP-only group, different hypothetical IOP thresholds were evaluated to determine the effect on numbers of referrals with positive outcomes missed and referrals with negative outcomes avoided. The influence of the participant's age on these was also determined.

Differences in mean age and IOP at referral between patients with positive and negative outcomes were evaluated using t-tests or the Mann–Whitney U test in normally and non-normally distributed data, respectively.

The referred patients were divided into three age groups (i.e. ≤44 years of age, 45–69 years of age and ≥70 years of age). Differences in the distribution of gender, positive outcome, diagnosis and glaucoma stage between the three age groups were analysed using Pearson's chi-squared test. Differences in median IOP between the same groups were analysed with the Kruskal–Wallis test.

All statistical analyses were performed using SPSS version 25 (IBM SPSS Statistics for Macintosh, Armonk, NY, USA). A p-value of ≤0.05 was used to define statistical significance.

Results

A total of 95 subjects (189 eyes) were included in the study (Fig. 1). The demographical and clinical characteristics of the study population are presented in Table 1. According to the definitions given above, the outcome of all referrals was positive in 33 cases (35%, 95% CI: 22–46%) and negative in 62 cases (65%, 95% CI: 55–75%). Of all referrals, 32 (34%) did not have any eye disease. Sixteen patients (17%) were presented with PEX, and three (3%) with pigment dispersion

syndrome. Of the 28 subjects diagnosed with glaucoma, 19 (68%) had primary open-angle glaucoma and nine (32%) had PEXG. The number of participants diagnosed as having glaucoma in the three age groups ≤44, 45–69 and ≥70 years were 6% ($n = 1$), 21% ($n = 10$) and 59% ($n = 17$), respectively (Table 1). No statistically significant differences were found between the three age groups regarding the median IOP reported by optometric practitioners or gender distribution (Table 1). The three age groups differed in diagnosis (p < 0.001), and in proportions of positive outcome (p < 0.001), according to Pearson's chi-squared test. Most patients with advanced VFD at presentation were found in the oldest age group (≥70 years), but this difference was not statistically significant (p = 0.264).

Of the 95 subjects investigated, 73 (77%) were IOP-only referrals, nine referrals (9%) included an ONH evaluation, four (4%) included a VF assessment and nine (9%) included both ONH and VF findings. The results of non-contact tonometry were included in 72 (76%) and GAT in eight referrals (8%). In the remaining 15 referrals (16%), the type of tonometer used was not stated. In the IOP-only group ($n = 73$), 29 (40%) had undergone more than one IOP measurement and 13 (18%) had undergone a CCT measurement. The results of the assessment of IOP, ONH and VF included in the referrals and the agreement with the results found at the visit to the Department of Ophthalmology are given in Table 2.

In the group of IOP-only referrals the PPV was 27% (95% CI: 16–38%). Referrals with only one IOP measurement ($n = 39$) had a PPV of 23% (95% CI: 9–37%), referrals with more than one IOP measurement ($n = 21$) had a PPV of 24% (95% CI: 3–45%) and referrals including a CCT measurement ($n = 13$) had a PPV of 46% (95% CI: 15–77%). The IOP-plus group ($n = 22$) had a PPV of 59% (95% CI: 36–82%).

In the IOP-only group, the participants with a positive outcome were on average 14 years older (70 ± 10.2 years versus 56 ± 15 years, p < 0.001, t-test) and had a 4 mmHg higher IOP at referral (30 ± 6 mmHg versus 26 ± 4 mmHg, p = 0.006, t-test), than those with a negative outcome. However, when analysing the
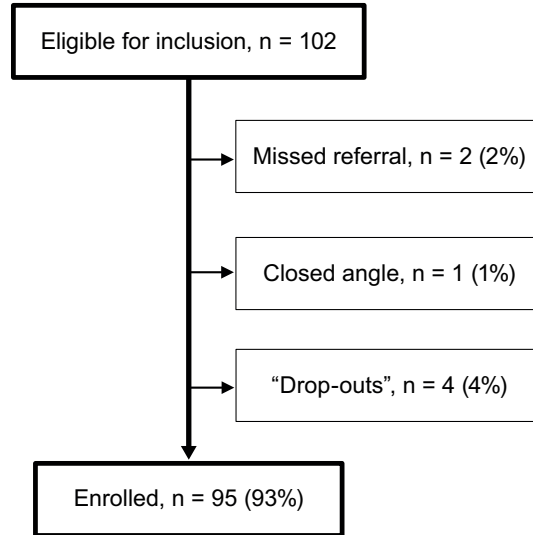
Fig. 1. Flow chart showing the number of eligible cases and reasons for exclusion. Patients were eligible if referred by optometric practitioners due to an intraocular pressure (IOP) of ≥21 mmHg and were over 18 years of age, not previously diagnosed with glaucoma nor showing symptoms of acute angle closure.

Table 1. Baseline characteristics and outcome of referred patients by age.

Baseline characteristics and outcome	All referrals (N = 95)	≤44 years (N = 18)	45–69 years (N = 48)	≥70 years (N = 29)	p-value
Age in years, median (range)	63 (22–85)	39 (22–44)	60 (48–69)	76 (70–85)	–
Gender, n (%)					
Female	47 (50%)	10 (56%)	23 (48%)	14 (48%)	0.848§
IOP in mmHg, median (range)	26 (19–41)	26 (19–30)	26 (21–36)	27 (21–41)	0.320#
Positive outcome, n (%)	33 (35%)	2 (11%)	11 (23%)	20 (69%)	**<0.0001§**
Diagnosis, n (%)					
Glaucoma	28 (29%)	1 (6%)	10 (21%)	17 (59%)	**<0.0001§**
Glaucoma suspect	5 (5%)	1 (6%)	1 (2%)	3 (10%)	
OHT	28 (29%)	4 (22%)	19 (40%)	5 (17%)	
No ocular disease	32 (34%)	12 (67%)	17 (35%)	3 (10%)	
Other pathology	2 (2%)	0 (0%)	1 (2%)	1 (3%)	
MD in worse eye in glaucoma patients, n (%)					
MD: early	16 (57%)	0 (0%)	6 (60%)	10 (59%)	0.264§
MD: moderate	5 (18%)	1 (100%)	2 (20%)	2 (12%)	
MD: advanced	7 (25%)	0 (0%)	2 (20%)	5 (29%)	

Data are presented as numbers (percentage). The median IOP was calculated using the value of the eye with higher IOP per patient documented in the referral. Positive outcome was defined as either definite glaucoma or glaucoma suspect. Glaucoma stage was defined according to Mills et al. (2006) using the mean deviation (MD) value in decibel (dB) of the worse eye measured at the clinic: early glaucoma – MD better than −6.01 dB, moderate glaucoma – MD −6.01 to −12.00 dB and advanced glaucoma – MD worse than −12.00 dB. p-values are calculated using either Pearsons Chi Square test (§) or Kruskal–Wallis test (#).
N = number, IOP = intraocular pressure, OHT = ocular hypertension.

Table 2. Agreement between IOP, ONH and VF assessments at the optometric practice and at the clinic.

Included in referral	IOP 189* (100%)		ONH 35 (19%)		VF 26 (14%)	
	<22 mmHg	≥22 mmHg	Normal	Suspicious	Normal	Suspicious
Assessment at the optometric practice	43	146	22	13	18	8
Confirmed at the clinical visit	30 (70%)	105 (72%)	16 (73%)	11 (85%)	13 (72%)	6 (75%)
	[56–84%]	[64–79%]	[43–80%]	[57–97%]	[48–89%]	[28–99%]

Data are presented as numbers (percentage) and [95% confidence interval]. Most eyes with an IOP < 22 mmHg were fellow eyes.
IOP = intraocular pressure, ONH = optic nerve head; VF = visual field.
* One participant had previously lost an eye in an accident.

oldest age group (≥70 years, n = 22) separately, the median IOP was similar for those with positive and negative outcome (26 mmHg, range 21–41 mmHg versus 25 mmHg, range 22–41 mmHg, p = 0.695, Mann–Whitney U test).

None of the subjects diagnosed as having glaucoma in the IOP-only group was younger than 45 years of age (Fig. 2), and all participants diagnosed as having glaucoma with an IOP below 28 mmHg measured by the optometric practitioners were aged 70 years or older (Fig. 2). The effects of different hypothetical age and IOP limits, as well as the combination of them, are shown in Figure 3.

Discussion

The overall predictive value of glaucoma referrals from optometric practitioners was low in this study, which is in accordance with recent reports (Founti et al. 2018b; Huang et al. 2020). The PPV increased, when changing the IOP threshold for IOP-only referrals. We also found that age was an important factor influencing the predictive value of referrals for glaucoma, as was expected.

US guidelines recommend eye care providers to measure IOP in individuals over 40 years of age (Prum et al. 2016), while our results indicate that glaucoma is rare in individuals younger than 45 years of age referred by optometric practitioners due to an elevated IOP. More than 20% of those referred based on IOP-only were younger than 45 years of age, but none of them was diagnosed as having glaucoma. The highest number of individuals with glaucoma and more advanced stages of glaucoma were found in the oldest age group (≥70 years). Furthermore, we found that no diagnosis of glaucoma would have been missed in the IOP-only group when using a higher IOP limit in individuals younger than 70 years, while maintaining the lower IOP threshold (≥22 mmHg) in patients aged 70 years or older. These results are in line with a previous study by Oskarsdottir and co-workers (Oskarsdottir et al. 2019) showing that the number of undetected glaucoma cases was somewhat higher in patients ≥70 years with an IOP of up to 24 mmHg, than in younger individuals with a similar IOP level. One possible explanation of this observation could be that the older the individual, the more susceptible the ONH is, even to moderately increased IOP levels (Steinhart et al. 2014; Jammal et al. 2020).

The prospective design of this study, with the same, double-blinded examiners, following a standard protocol at all study visits, is a strength of the study, as was the fact that nearly all the eligible subjects could be included. Although we believe that this population is representative of the Swedish population in general, the results are probably not applicable to other European countries due to differences in referral strategies. One weakness of our study is the relatively small sample size. A second is the fact that our hospital is not the only referral unit for patients living in the catchment area. Several private ophthalmologists work in the same region, and it is therefore reasonable to assume that a significant number of subjects were not referred to our hospital. In Sweden, ophthalmologists in the private sector and at the glaucoma outpatient departments at hospitals provide all kinds of secondary medical eye care and optometric practitioners can choose to refer glaucoma suspects to either. It is not known whether referrals to private practitioners differed in any significant way from those in this study. Nevertheless, the majority of the optometric practitioners that had referred patients to our hospital reported doing so for geographical reasons, or because of the
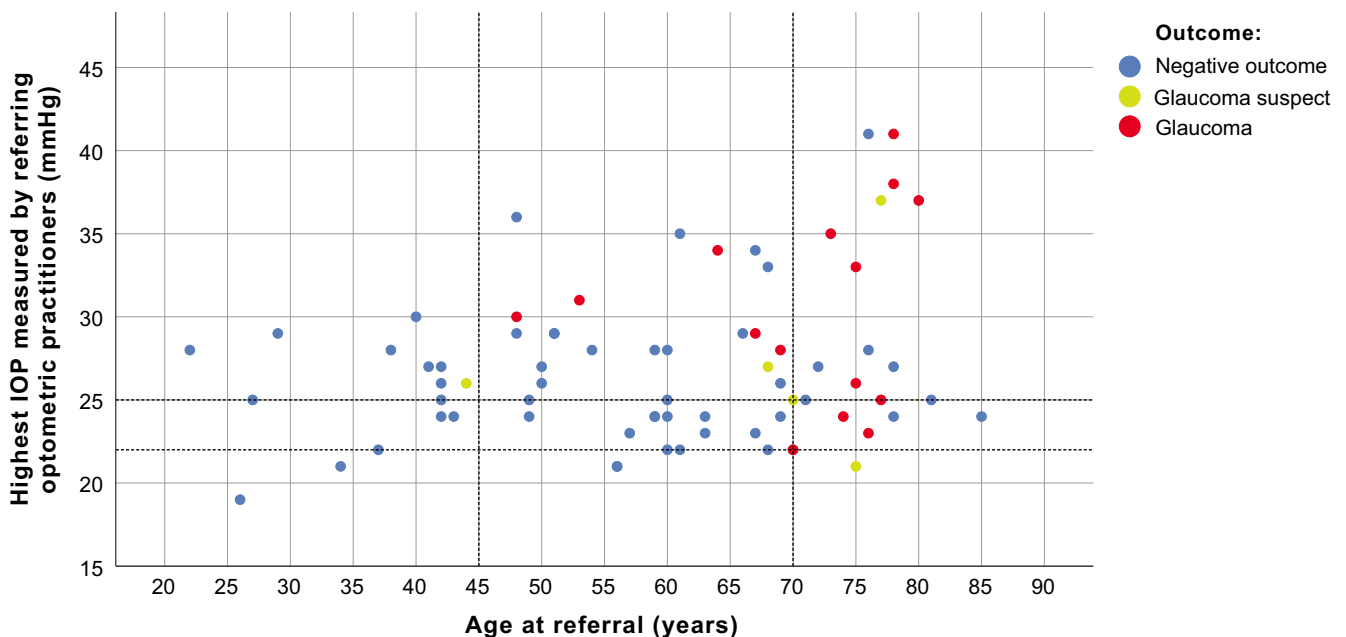

Fig. 2. Outcome of referral according to the intraocular pressure (IOP) and age at referral in IOP-only referrals (N = 73). The youngest patient diagnosed as having glaucoma was 48 years. Most glaucoma patients were found in the age group ≥70 years. Younger patients diagnosed with glaucoma presented with a clearly elevated IOP, whereas older patients with glaucoma more often had only moderately elevated IOP. The horizontal and vertical dotted lines indicate different hypothetical age and IOP limits applied for referral.
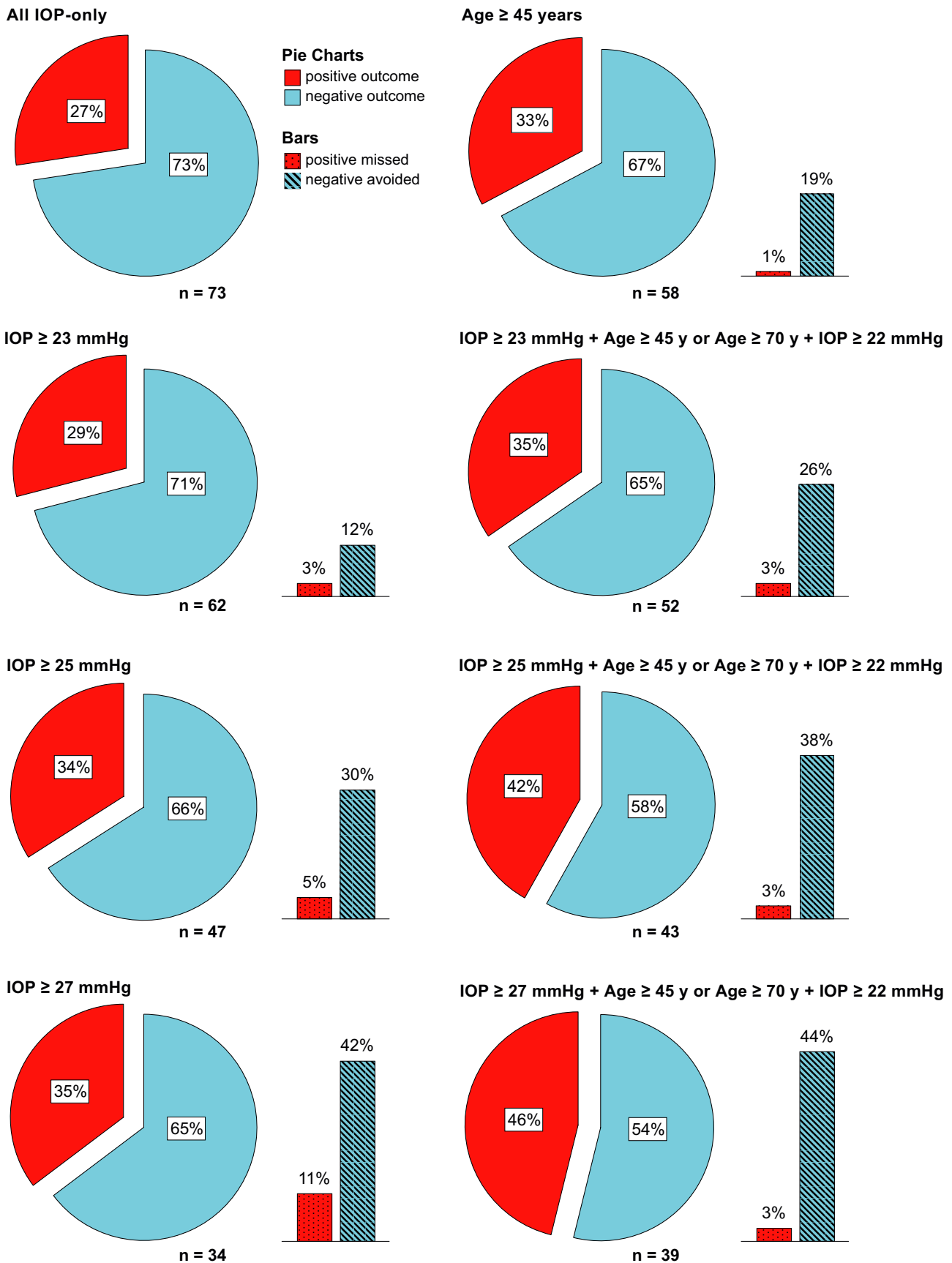
Fig. 3. Outcome of intraocular pressure (IOP)-only referrals and changes in referrals with positive outcome missed and referrals with negative outcome avoided when applying different hypothetical age and IOP thresholds for referral. With an IOP limit of ≥25 mmHg in the age group 45–69 years and an IOP limit of ≥22 mmHg in the older age group (≥70 years), 28 (28 of 73, 38%) referrals with negative outcome would have been avoided. Only two (two of 73, 3%) referrals with positive outcome (both glaucoma suspects) would have been missed, while no definite cases of glaucoma would have been missed.

patient's wish to be referred to the hospital. However, a few optometric practitioners said that they chose to refer cases more likely to be glaucoma to our hospital than to private ophthalmologists. Hence, the real predictive value of referrals may be even lower than reported here. Another limitation is that it was not possible to draw any conclusions on the negative predictive value of referrals from the findings of the present study.

Intraocular pressure (IOP)-only referrals with only moderately elevated IOP are known to have a low predictive value concerning glaucoma suspects (Ratnarajan et al. 2013). We also found a low PPV for IOP-only referrals. Based on the current clinical practice at our hospital, OHT was defined using CCT-adjusted IOP values for patients without any signs of glaucoma and with an unadjusted IOP between 22 to 27 mmHg. The Ehlers correction factor was used as the same is used in our hospital. We are well aware that there is, as yet, no adequately validated CCT algorithm and that the European Glaucoma Society does not recommend this practice. However, we used this approach to make the results transferable to our hospital. Using IOP measurements without CCT correction would have increased the number of participants with OHT by a further 10 cases.

It has previously been reported that combining the results from different examinations leads to an increase in correct glaucoma referrals (Tuck & Crick 1991; de Vries et al. 2012; Keenan et al. 2015; Founti et al. 2018b). We found a similar effect, namely, a higher predictive value of referrals including VF and/or ONH findings.

Founti and co-workers (Founti et al. 2018b) proposed an IOP threshold of at least 27 mmHg as a requirement for IOP-only referrals (using UK referrals only) and found that no glaucoma case would have been missed using this limit. In the present study, five patients with glaucoma and three patients with suspected glaucoma would have been missed when using a similar IOP limit. One possible explanation of this difference could be that individuals referred without any additional assessment had higher IOPs in the UK than those in our study. Besides, the lower prevalence of PEXG in the UK compared to Sweden might also have influenced the different results.

With limited resources, it is of great importance to prioritize those at significant risk of visual disability and thus loss of vision-related quality of life (Tuulonen et al. 2016). As advanced VFD at presentation is one of the major risk factors for glaucoma-related blindness (Grodum et al. 2002; Forsman et al. 2007; Peters et al. 2014; Saunders et al. 2014), resources should be directed towards identifying cases of glaucoma. Evidence-based national guidelines are needed in Sweden to improve the outcome of glaucoma referrals.

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Correspondence:
Dorothea Peters, MD, PhD
Department of Clinical Sciences Malmö,
Ophthalmology
Skåne University Hospital
Lund University
SE-205 02 Malmö
Sweden
Tel: +46 40 336152
Fax: +46 40 336212
Email: dorothea.peters@med.lu.se