# Late presentation of advanced glaucoma patients; missed opportunities for diagnosis

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## ABSTRACT

**Objective:** This study aimed to determine the proportion of late glaucoma presenting patients who have had previous contact with a primary eye health worker prior to presentation.
**Methods:** A systematic review and analysis was performed on ten studies with a total of 47,367 study participants identified meeting the inclusion and exclusion criteria. A meta- analysis of proportions was conducted on the late presenting glaucoma patients as well as the proportion of those that had previous contact with a primary eye care worker prior to diagnosis. We combined a narrative synthesis and quantitative (statistical pooling) approach for the synthesis of the extracted studies' information.
**Results:** The pooled proportion of late presenting glaucoma patients was 0.325 (95% CI 0.178 -0.493). Out of all the late presenting glaucoma patients, n=2967, 96% (CI 0.85- 1.00) had previous contact with a primary eye health worker. The commonest type of primary eye health care workers identified were optometrists, general practitioners, ophthalmic nurses and technicians.
**Conclusion:** Out of all the late presenting glaucoma patients, a high number have previously been referred by a primary eye care worker. This represents a huge opportunity for directing effort at primary eye care level to identify and appropriately refer glaucoma patients for timely and definitive care.

**Key words:** Advanced glaucoma, Late presentation, Refer, Optometrist, Screen

## INTRODUCTION

Glaucoma is a group of eye diseases which is characterised by progressive optic nerve damage and visual field loss. It is the leading cause of irreversible blindness worldwide and has highest prevalence in low income regions[1].The number of people with glaucoma worldwide is projected to increase to 111.8 million in 2040, and affecting more people in Africa and Asia[2]. Currently, in Africa, glaucoma contributes to 13.47% of all causes of blindness in Sub Saharan Africa[3], and with a prevalence of 4% in people aged above 40 years[4].

This disease can be screened early on in its asymptomatic stage and therefore avert irreversible blindness. The fact that glaucoma is typically asymptomatic, patients are usually unaware of the continuing damage, and most especially unaware too of the irreversible nature of the disease.

There has been evidence that unfortunately, most of the glaucoma patients are first diagnosed with advanced disease, more so in sub-Saharan Africa[4] and factors such as limited access to facilities, cost of care, lack of awareness have been attributed[5,6]. As much as late glaucoma presentation is a worldwide concern, African nations have been noted to have more patients presenting with advanced glaucoma as opposed to patients in developed countries[5].

Classification of glaucoma in research largely depends on the level of peripheral vision dysfunction as assessed by automated visual field assessment. This is referred to as functional damage assessment. Additionally, optic disc structural damage assessment is also done as part of the triad of glaucoma diagnosis[7]. However, either of the two assessments in isolation can also be used to grade glaucoma[4,7]. For the purposes of this study, either of the grading system, functional or structural, was used for advanced glaucoma case definition as well as staging.

Late presentation is described where patients present for the first time with advanced glaucoma features at the diagnosis centre[6,9,10].

Primary eye care workers are trained to offer eye health promotion, prevention, treatment and rehabilitation. This as in primary examination, diagnosis and eye health education to patients at the primary health facilities as well as in the community. In most countries, they include optometrists, opticians, ophthalmic technicians, ophthalmic nurses, ophthalmic clinical officers, assistant medical officers and general practitioners[11]. Their

distribution and particular job description varies from country to country depending on development status as well as policy pattern[12].

## MATERIALS AND METHODS

The objective of this review was to analyse the proportion of late glaucoma presenting patients who have had previous contact with a primary eye health worker prior to presentation.

This review tested the hypothesis that patients with advanced glaucoma at initial presentation usually have had previous contact with a primary eye health care worker.

*Eligibility criteria:* All studies with advanced primary glaucomas in adults, who are presenting late at initial presentation as defined by either structural disc damage and/or functional visual field damage described in either eye[7].

The study population was the patients identified in the study as having advanced glaucoma as defined by the extent of visual field loss through perimetry testing using a 24-2 or 30-2 strategy. This extent uses the the Hodapp–Parrish–Anderson (HPA) Glaucoma classification[10].

The studies would include observational, case control, cross- sectional, cohort and randomised control trials. Record of previous contact with the eye health worker had to be present, as in optometrist visit, prior referral, or previous screening depending on the particular study in either hospital or community setting.

*Exclusion criteria:* Included case reports, studies with patients already on glaucoma treatment, or glaucoma suspects.

*Search strategy:* We followed the PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (Last updated February 27, 2020) statement for guiding our reporting of methods[13].The search schema was designed consultatively by the two main reviewers. Various databases were searched by using the key words of the concept areas. These databases include Medline, Web of Science, Pubmed and Embase using the Ovid platform. Other search methods included citation tracking of the identified papers by browsing reference lists. All searches were done without date, language or study design restrictions. The search yielded published papers, reviews and conference abstracts. Last search date was June 2022. No search filters were employed. No additional data was sought from the authors of the studies reviewed as it was not required. The full search strategy and history is summarised below in Appendix 1.

**Appendix 1:** Database specific search strategy

| Database searched Through Ovid Interface | Search strategy/ History |
|---|---|
| | Database: Ovid MEDLINE(R) <1946 to March Week 3 2022><br>Search Strategy:<br>---------- |
| | 1 exp Glaucoma, Open-Angle/ or Glaucoma/ or exp Low Tension Glaucoma/ (53367) |
| | 2 exp Visual Fields/ (31912) |
| | 3 exp Optic Disk/ab, an, dg, pa, ul [Abnormalities, Analysis, Diagnostic Imaging, Pathology, Ultrastructure] (7134) |
| | 4 exp Late Onset Disorders/di, pa, pc, th [Diagnosis, Pathology, Prevention & Control, Therapy] (109) |
| | 5 exp Time-to-Treatment/cl [Classification] (2) |
| | 6 exp Optometrists/ (169) |
| | 7 screen*.mp. (827404) |
| | 8 reffer*.mp. (126) |
| | 9 community.mp. or Residence Characteristics/ (584460) |
| | 10 ophthalmic* nurse.mp. (76) |
| | 11 clinical officer.mp. (80) |
| | 12 optician.mp. (119) |
| | 13 optician.mp. or Vision Screening/ (2489) |
| | 14 first.mp. (2358291) |
| | 15 initial.mp. (727400) |
| | 16 1 or 2 or 3 (81472) |
| | 17 4 or 5 (111) |
| | 18 7 or 8 or 9 or 10 or 11 or 12 or 13 (1377074) |
| | 19 14 or 15 (2954509) |
| | 20 16 and 17 (1) |
| | 21 16 and 18 (3386) |
| | 22 16 and 17 and 18 (0) |
| | 23 16 and 17 and 18 and 19 (0) |

| Database searched Through Ovid Interface | Search strategy/ History |
|---|---|

| # | Query | Results from 26 Mar 2022 |
|---|---|---|
| 1 | exp Glaucoma, Open-Angle/ or Glaucoma/ or exp Low Tension Glaucoma/ | 53,367 |
| 2 | exp Visual Fields/ | 31,912 |
| 3 | exp Optic Disk/ab, an, dg, pa, ul [Abnormalities, Analysis, Diagnostic Imaging, Pathology, Ultrastructure] | 7,134 |
| 4 | exp Late Onset Disorders/di, pa, pc, th [Diagnosis, Pathology, Prevention & Control, Therapy] | 109 |
| 5 | exp Time-to-Treatment/cl [Classification] | 2 |
| 6 | exp Optometrists/ | 169 |
| 7 | screen*.mp. | 827,404 |
| 8 | reffer*.mp. | 126 |
| 9 | community.mp. or Residence Characteristics/ | 584,460 |
| 10 | ophthalmic* nurse.mp. | 76 |
| 11 | clinical officer.mp. | 80 |
| 12 | optician.mp. | 119 |
| 13 | optician.mp. or Vision Screening/ | 2,489 |
| 14 | first.mp. | 2,358,291 |
| 15 | initial.mp. | 727,400 |
| 16 | 1 or 2 or 3 | 81,472 |
| 17 | 4 or 5 | 111 |
| 18 | 7 or 8 or 9 or 10 or 11 or 12 or 13 | 1,377,074 |
| 19 | 14 or 15 | 2,954,509 |
| 20 | 16 and 17 | 1 |
| 21 | 16 and 18 | 3,386 |
| 22 | 16 and 17 and 18 | 0 |
| 23 | 16 and 17 and 18 and 19 | 0 |

exp Glaucoma, Open-Angle/ or Glaucoma/ or exp Low Tension Glaucoma/
exp Visual Fields/
exp Optic Disk/ab, an, dg, pa, ul [Abnormalities, Analysis, Diagnostic Imaging, Pathology, Ultrastructure]
exp Late Onset Disorders/di, pa, pc, th [Diagnosis, Pathology, Prevention & Control, Therapy]
exp Time-to-Treatment/cl [Classification]
exp Optometrists/
screen*.mp.
reffer*.mp.
community.mp. or Residence Characteristics/
ophthalmic* nurse.mp.
clinical officer.mp.
optician.mp.
optician.mp. or Vision Screening/
first.mp.
initial.mp.
1 or 2 or 3
4 or 5

7 or 8 or 9 or 10 or 11 or 12 or 13
14 or 15
16 and 17
16 and 18
16 and 17 and 18
16 and 17 and 18 and 19

Database:
Ovid MEDLINE(R) <1946 to March Week 3 2022>

| Database searched Through Ovid Interface | Search strategy/ History |
|---|---|

| # | Query | Results from 26 Mar 2022 |
|---|---|---|
| 1 | late presentation.mp. | 2,351 |
| 2 | exp Optometrists/ed [Education] | 8 |
| 3 | initial diagnosis.mp. | 15,464 |
| 4 | exp Glaucoma, Open-Angle/ or advanced glaucoma.mp. | 16,084 |
| 5 | 1 and 2 and 3 and 4 | 0 |

late presentation.mp.
exp Optometrists/ed [Education]
initial diagnosis.mp.
exp Glaucoma, Open-Angle/ or advanced glaucoma.mp.
1 and 2 and 3 and 4

Database:
Ovid MEDLINE(R) <1946 to November Week 1 2021>

| # | Query | Results from 14 Nov 2021 |
|---|---|---|
| 1 | exp Glaucoma/ or advanced glaucoma.mp. | 55,967 |
| 2 | late presentation.mp. | 2,279 |
| 3 | Glaucoma/ep and Glaucoma/pc and Glaucoma/sn and Glaucoma/su and Glaucoma/th [Epidemiology,Prevention&Control,Statistics& Numerical Data,Surgery,Therapy] | 0 |
| 4 | exp Glaucoma/ | 55,925 |
| 5 | 1 and 2 | 31 |

exp Glaucoma/ or advanced glaucoma.mp.
late presentation.mp.
Glaucoma/ep and Glaucoma/pc and Glaucoma/sn and Glaucoma/su and Glaucoma/th [Epidemiology,Prevention&Control,Statistics& Numerical Data,Surgery,Therapy]
exp Glaucoma/
1 and 2

Database:
Embase<1980 to 2022 Week 13>

| # | Query | Results from 8 Apr 2022 |
|---|---|---|
| 1 | detect*.mp. | 3,353,377 |
| 2 | glaucoma/ or glaucoma.mp. | 94,845 |
| 3 | reffer*.mp. | 857 |
| 4 | 1 and 2 and 3 | 0 |
| 5 | optic disc change*.mp. | 224 |
| 6 | 3 and 5 | 0 |
| 7 | 1 and 5 | 59 |
| 8 | community/ or community.mp. | 786,108 |
| 9 | screen*.mp. | 1,488,348 |
| 10 | 2 or 5 | 94,896 |
| 11 | 8 and 9 and 10 | 298 |

| Database searched Through Ovid Interface | Search strategy/ History |
|---|---|
| | detect*.mp.<br>glaucoma/ or glaucoma.mp.<br>reffer*.mp.<br>1 and 2 and 3<br>optic disc change*.mp.<br>3 and 5<br>1 and 5<br>community/ or community.mp.<br>screen*.mp.<br>2 or 5<br>8 and 9 and 10 |
| | Database:<br>Ovid MEDLINE(R) <1946 to April Week 2 2022> |

| # | Query | Results from 15 Apr 2022 |
|---|---|---|
| 1 | Advanced glaucoma.mp. | 736 |
| 2 | blind*.mp. | 366,411 |
| 3 | refer*.mp. | 1,009,361 |
| 4 | primary eye.mp. | 409 |
| 5 | optometr*.mp. | 7,858 |
| 6 | 3 or 4 or 5 | 1,016,518 |
| 7 | 1 and 2 | 61 |
| 8 | 6 and 7 | 9 |
| 9 | late detection.mp. | 466 |
| 10 | nurs*.mp. | 733,096 |
| 11 | 3 or 4 or 5 or 10 | 1,721,130 |
| 12 | 8 and 11 | 9 |

Advanced glaucoma.mp.
blind*.mp.
refer*.mp.
primary eye.mp.
optometr*.mp.
3 or 4 or 5
1 and 2
6 and 7
late detection.mp.
nurs*.mp.
3 or 4 or 5 or 10
8 and 11

Manual search using the Schema was done in Pubmed, and Web of Science up to May 2022 but no additional studies were identified. Citation tracking was done to add 3 studies to the screening

*Data extraction:* Total number of records identified were 683. The records searched were then exported to Covidence software for screening and data extraction, where one hundred and two duplicates were removed.

Each study abstract was screened independently by the two main reviewers. Any outstanding disagreements were arbitrated by a third reviewer. The identified articles subsequently underwent full text review similarly using the inclusion and exclusion criteria. The flowchart is provided in Figure 1.

Ten studies were finally arrived at for data extraction after agreement by the reviewers. All the ten studies had been independently assessed by the two main reviewers.
Quality assessment: We conducted a quality assessment of the included studies using the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) guidelines[14], as the included studies were largely observational. The two primary areas that were of importance were; adequately described study participants with population identification, as well as outcome data as in appropriate methods of arriving at study findings. This is elaborated in Appendix 2. The risk of bias was graded as low, moderate and high risk of bias.

**Appendix 2:** Guidelines used for assessing risk of bias as derived from the STROBE guidelines

| Potential Bias | Items to be Considered | Risk ratings |
|---|---|---|
| **Study Participants (STROBE Item 6)**<br>Does the study have the population of interest? | There is adequate description of the study population of interest | **High risk of bias**<br>No grading classification is mentioned |
| | Description of the extent of which identification of advanced glaucoma patients is considered<br>Is Humphrey Visual field (HVF) used? | **Moderate risk of bias**<br>Only one criteria are used, as in either optic disc criteria or median deviation (MD) |
| | Is median deviation highlighted? | **Low risk of bias**<br>Both perimeter with Humphrey visual field analyser testing as well as optic disc assessment |
| | Is optic disc assessment done?<br>Have the study participants been previously managed for glaucoma? | |
| **Descriptive data (Item 14a)**<br><br>Are characteristics of study participants adequately detailed?<br><br>Is geographical, clinical, and demographic information detailed? | Well detailed description of the study clinical setting and context | **High risk of bias**<br>Study setting not well described<br><br>**Moderate risk of bias**<br>Study setting described but not to detail on geographical zone or clinical setting<br><br>**Low risk of bias**<br>Clinical and geographical context well outlined |
| **Outcome data (Item 15)**<br><br>Is the description of the participating primary eye care workers adequately done?<br><br>Is there adequate demonstration of the referral of an unconfirmed glaucoma participant | Number of advanced glaucoma patients who are referred is clearly arrived at to allow for reproducible extraction<br><br>Tertiary eye hospital or ophthalmologist arrival at a definite diagnosis is demonstrated<br><br>Is the role of the primary eye care worker in patient identification clearly explained?<br><br>Detailed demonstration that referral pathway is present | **High risk of bias**<br>No primary eye care worker identified, nor their role in referring an advanced glaucoma patient<br><br>**Moderate risk of bias**<br>Referral pattern or primary eye care worker role not adequately demonstrated<br><br>**Low risk of bias**<br>Role of Primary eye care workers clearly demonstrated as well as their contact with advanced glaucoma patient referral |

*Data synthesis:* The extracted data was put up in a table of included studies. Proportional meta-analysis was undertaken with the statistical software R for the main outcome of interest. All meta - analysis used the random effects model that considers both between studies and within studies variances into account. We did not use the fixed effect model as differences among observed effect sizes were not solely due to within-study variance, but as a result of studies performed in different settings which caused the true effect sizes to vary[15].

A point estimate was arrived at with 95% confidence interval. In testing for heterogeneity, and inconsistencies, tau- squared test, and I2 were used.

Subgroup analysis was also undertaken to determine whether the observed heterogeneity was due to a particular effect. Similarly, tau- squared test, Q test and $I^2$ were used. For the subgroup analysis the on meta-analytical methods used were:

- Inverse variance method
- DerSimonian-Laird estimator for tau^2
- Jackson method for confidence interval of tau^2 and tau
- Freeman-Tukey double arcsine transformation
- Clopper-Pearson confidence interval for individual studies

We combined a narrative synthesis and quantitative (statistical pooling) approach for the synthesis of the extracted studies' information. This was done according to the guidance approach provided[16]. This approach was arrived at as the heterogeneity of the studies included was large, that is, greater than 75%.

A stratified narrative sub analysis was done on how the late presenting patients vary by geographic region, study design, diagnostic criteria for determining late stage of glaucoma (HVF vs disc only), and type of primary referring eye care worker.

## RESULTS

Ten studies were recruited from the search. The screening process is shown in Figure 1.These studies[5,17-25] yielded a cumulative total of 47,367 study participants. Study participants ranged from 32,918 to 84 patients per study. The characteristics of the selected papers are shown in

Table 1. The studies cut across various countries. Four studies had participants from United Kingdom, three from across Africa, and one from Australia, Canada, India, and Sweden each.All of the studies were observational.

**Table 1:** Description of included studies

| Study ID | Country | Study design | Investigation | Participants | Glaucoma patients | Late presenters | Referred |
|---|---|---|---|---|---|---|---|
| Verma 2014 | Canada | Cohort study | Optic disc | 247 | 77 | 16 | 16 |
| Fraser 2001 | UK | Case control study | HVF, optic disc | 220 | 220 | 110 | 110 |
| Olawoye 2013 | Nigeria | Cross sectional study | HVF | 653 | 653 | 370 | 370 |
| Jeganathan 2015 | UK | Retrospective | HVF | 84 | 84 | 23 | 23 |
| Azuara-Blanco 2016 | UK | Comparative diagnostic evaluation | HVF | 943 | 158 | 28 | 28 |
| Green 2018 | Australia | Retrospective | HVF | 188 | 188 | 4 | 4 |
| Jones 2020 | Tanzania, UK | Retrospective extraction from medical records | HVF | 10766 | 10766 | 2,166 | 2166 |
| Marco 2021 | Kenya | Cohort study | Optic nerve criteria | 1187 | 42 | 23 | 23 |
| Heijl 2013 | Sweden | Cross sectional study | HVF, optic disc assesment | 32,918 | 406 | 163 | 134 |
| Odayappan 2021 | India | Cross sectional study | Optic disc criteria | 161 | 161 | 64 | 9 |

**Table 2:** Table showing outcome of quality assessment and justification for rating

| Study | Risk of participants bias | Risk of descriptive data bias | Risk of outcome data bias |
|---|---|---|---|
| Azuara-Blanco 2016 | Low risk<br>Detailed description of imaging devices that were used<br><br>Assessment using Humphrey Visual Field, 24-2 SITA strategy and classification by median deviation<br><br>Optic disc assessment by using Optical Coherence Topography (OCT) | Low risk<br>Study setting adequately described; Five NHS hospitals<br>Participant recruitment process well demonstrated<br>Comparative diagnostic evaluation | Low risk<br>Confirmation of advanced glaucoma patients who are presenting late is adequately done |
| Fraser 2001 | Moderate risk<br>Fist presentation mentioned<br>Eligibility criteria well outlined with detail of Humphrey visual field used as well as optic disc assessment<br><br>The late presenters, described by visual field loss from fixation (this being a field loss within five degrees of fixation and greater than thirty degrees in one or both eyes.<br>Participants excluded who had difficulty performing visual field test and therefore considered as moderate risk of bias | Low risk<br>Study setting well described as three independent eye departments<br><br>Participant recruitment process well demonstrated<br><br>Case control | Low risk<br>Principle referring primary eye workers mentioned<br>Late presenters can be arrived at |
| Green 2018 | Visual field and optic disc assessment done<br>Classification of advanced glaucoma done by assessing median deviation (MD)<br>Study had only initial presenting patients at the hospital and eye centre<br>Some participants however is mentioned had previously been managed by another practitioner | Moderate r isk<br>Study setting in hospital as part of a new model of care | Low risk<br>Referring primary care worked mentioned<br>Late presenters are identifiable |

| Study | Risk of participants bias | Risk of descriptive data bias | Risk of outcome data bias |
|---|---|---|---|
| Heijl 2013 | Low risk<br>Recruitment of participants well described<br>Perimetry done as well as optic disc assessment<br>Median deviation (MD) used for classification of glaucoma | Low risk<br>Population based screening with diagnosis at a tertiary eye centre<br>Referral system clearly outlined | Low risk<br>Primary eye care worker in Early Manifest Glaucoma Trial secondary paper; ophthalmic technicians<br>Late presenters well identified |
| Jeganathan 2015 | Low risk<br>Participants well described as first hospital visit<br>Perimetry done as well as optic disc assessment<br>Median deviation (MD) used for classification of glaucoma<br>Advanced glaucoma patients well described | Low risk<br>Hospital based with referral pattern/ process well outlined | Low risk<br>Primary referring eye workers mentioned distinctly<br>Late presenters well outlined |
| Jones 2020 | Low risk<br>Participants well described at the very first appointment<br>Perimetry done as well as optic disc assessment<br>Median deviation (MD) used for classification of glaucoma<br>Advanced glaucoma patients well described | Moderate risk<br>Study setting adequately described in two distinct geographical zones therefore considered as moderate risk of bias | Moderate risk<br>Late presenters well outlined<br>Referral by ophthalmic technician<br>Referral strategy not elaborately outlined and therefore considered as moderate risk of bias |
| Marco 2021 | Moderate risk<br>Participants well described as first presentation<br>Optic nerve criteria is only used for classification of glaucoma and therefore considered as moderate risk | Low risk<br>Study setting adequately described | Low risk<br>Detailed demonstration that referral pathway is present up to the tertiary eye centre<br>Role of primary eye care worker outlined |
| Odayappan 2021 | Moderate risk<br>Participants well described as first presentation<br>Perimetry done, but not for all patients, using a Humphrey Field Analyser as well as optic disc assessment<br>Optic nerve criteria used for classification of glaucoma<br>Advanced glaucoma patients are well derived | Low risk<br>Study setting well described as clinic patients | Low risk<br>Referral pathway clearly described, done by various primary eye care centres in the referring centre<br>Advanced glaucoma patient number clearly identified |
| Olawoye 2013 | Low risk<br>Participants well described as first presentation<br>Perimetry done as well as optic disc assessment<br>Median deviation (MD) used for classification of glaucoma severity<br>Advanced glaucoma patients well described | Low risk<br>Study setting well outlined from referral centre to the base hospital | Low risk<br>Referral pathway clearly outlined as well as the referring team |
| Verma 2014 | High risk<br>Exclusion criteria was patients with already advanced glaucoma as at the screening site<br>Perimetry done as well as optic disc assessment | Low risk<br>Study design as collaborative tele glaucoma programme<br>Clinical setting well outlined | Low risk<br>Clinical referral pathways were well outlined |

**Figure 1:** Flowchart of records search process

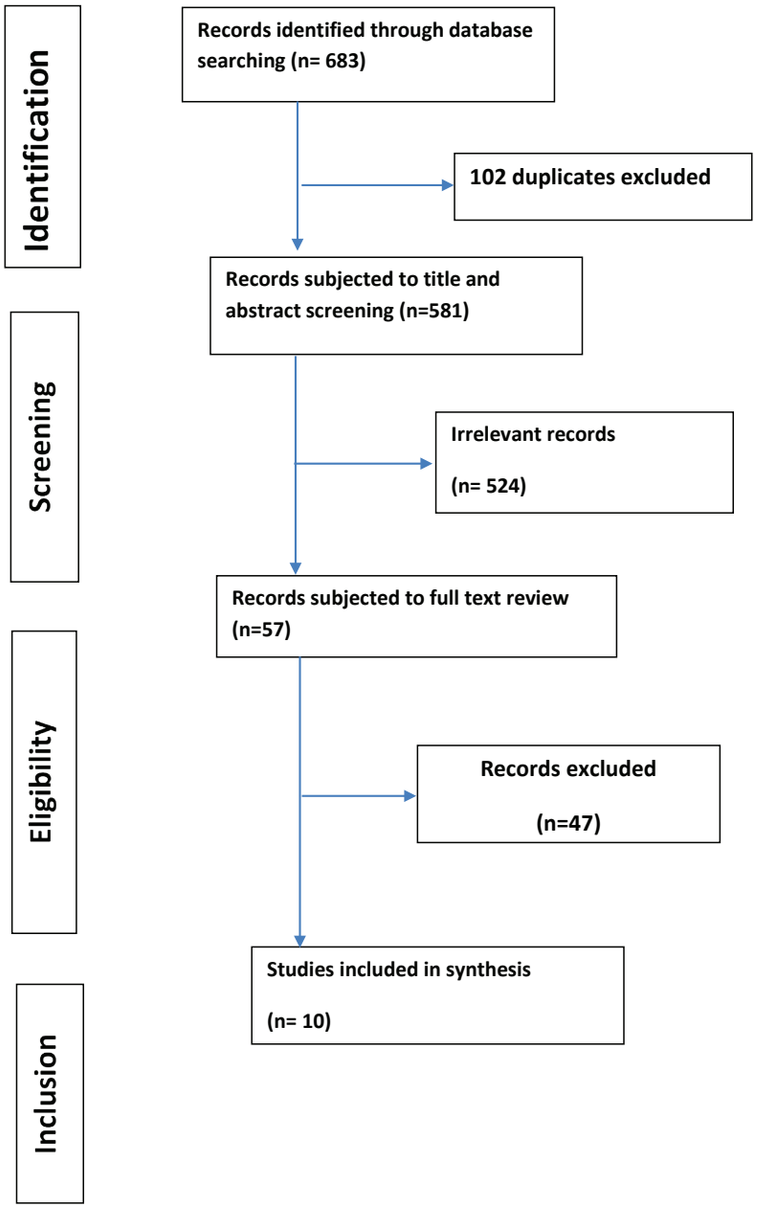
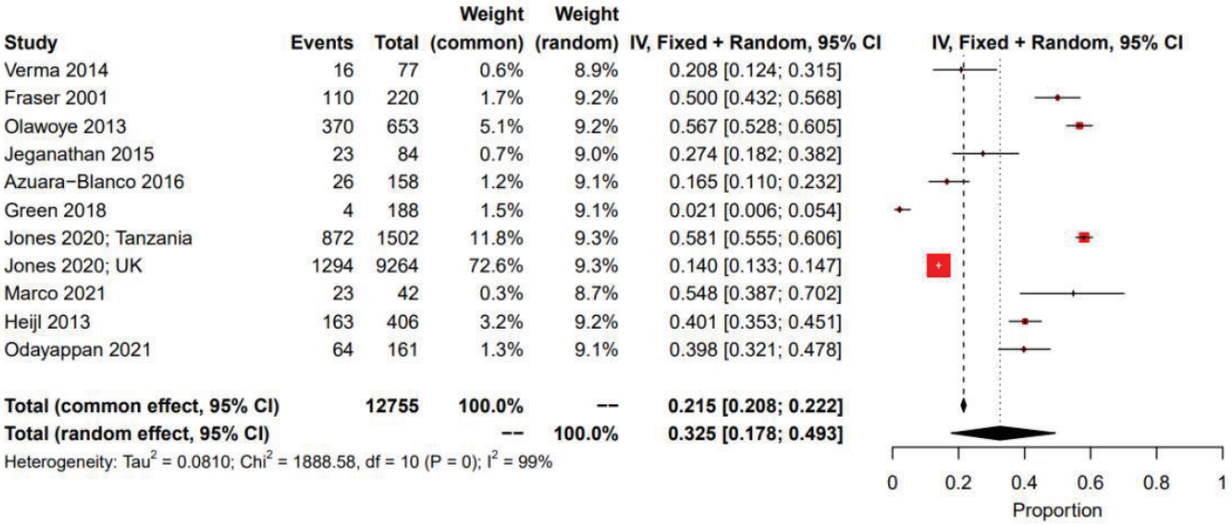



**Figure 2:** Forest plot of meta- analysis of proportion of late presenting glaucoma patients



The pooled proportion of late presenting glaucoma patients was 0.325 (95% CI 0.178 -0.493) (Figure 1). However due to the large statistical heterogeneity identified, this value should be interpreted with caution. Total heterogeneity, as estimated by $tau^2$, was 0.0810. The late presenting glaucoma patients from the included studies, ranged from to 2.1% to 58.06%. Out of all the late presenting glaucoma patients (n=2967), 96% (CI 0.85- 1.00) had previous contact with a primary eye health worker. The pooled proportion was 0.96 (0.85-1) (Figure 2). From the weighted proportion of each study, the proportion of advanced glaucoma patients who were referred did not vary significantly between the countries represented in the summary. There was significant heterogeneity of the included studies as in the $I^2$ greater than 95% in the proportion meta- analyses. A narrative synthesis was therefore employed to allow investigation of the observed heterogeneity. The primary eye health care workers identified were mostly optometrists in seven studies, general practitioners in four studies, ophthalmic technician and ophthalmic nurse in three studies each. Two studies reported screening as done by a team of primary eye care workers in the community and therefore referral was evaluated as from 'other' source.

We categorised and analysed the study in subgroups. The subgroups were based on geographical location of the study, type of study design used, and the method of classification of advanced glaucoma (Humphrey Visual Field vs optic disc criteria). All the subgroups analysed showed over 90% heterogeneity. The $I^2$ test was preferred as the one to quantify heterogeneity as is the most reliable in meta-analysis of less than ten studies[26]. The number of studies done in each subgroup analysis, pooled proportion of advanced glaucoma with its accompanying confidence interval is shown in Figures 5- 7. There was no observed effect when we analysed effect of the geographical region where the studies were carried out (Figure 5).

**Figure 3:** Forest plot of meta- analysis of proportion of patients who were referred by a primary eye care worker

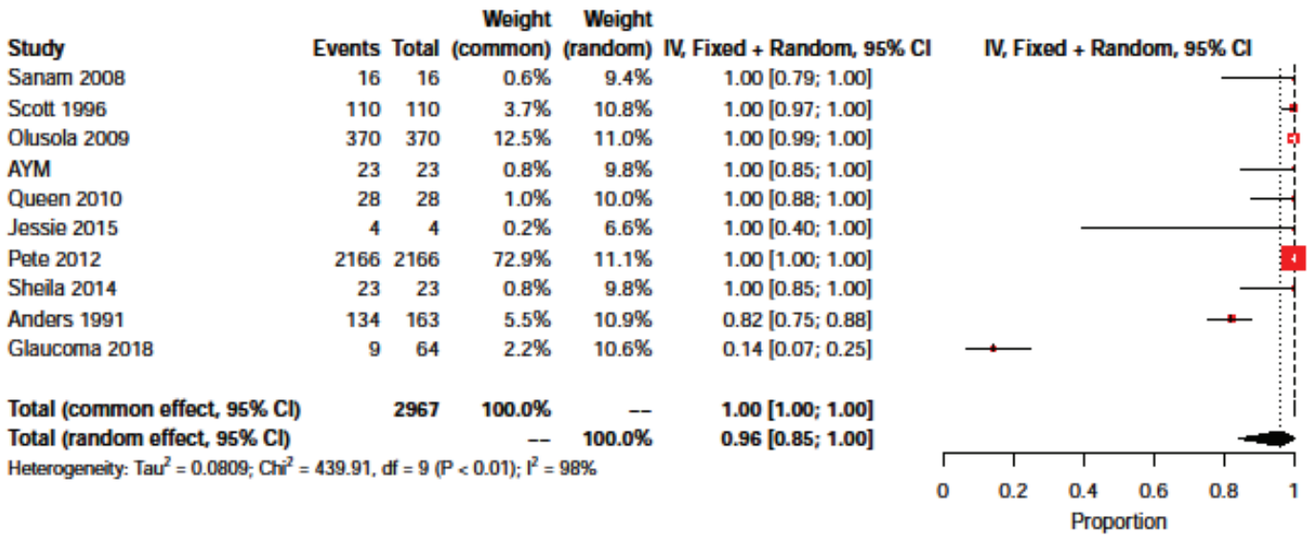



**Figure 4:** Frequency bar chart showing type of primary eye care worker that referred advanced glaucoma patients

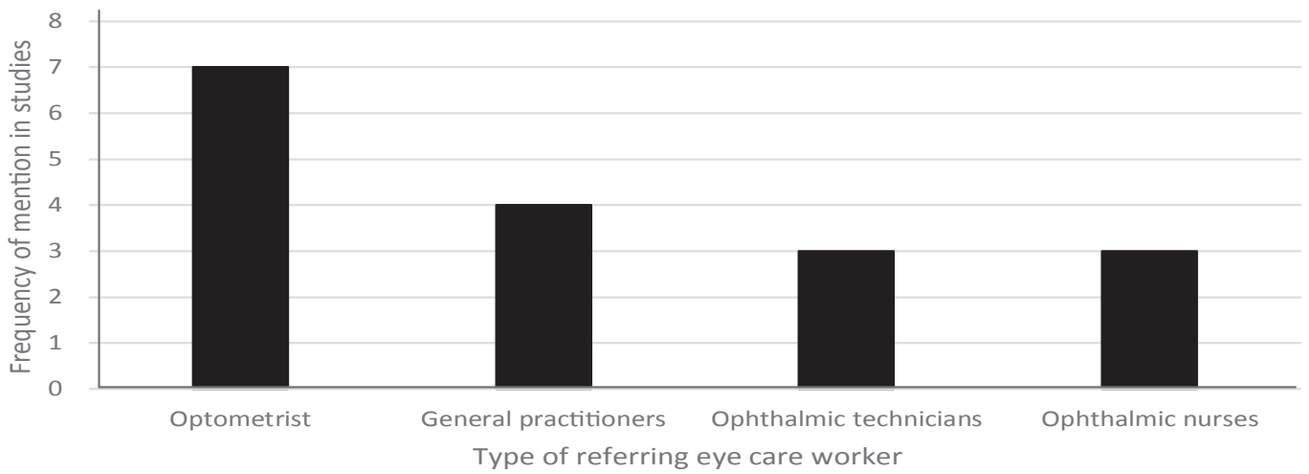


**Figure 5:** Results of subgroup analyses based on geographical location

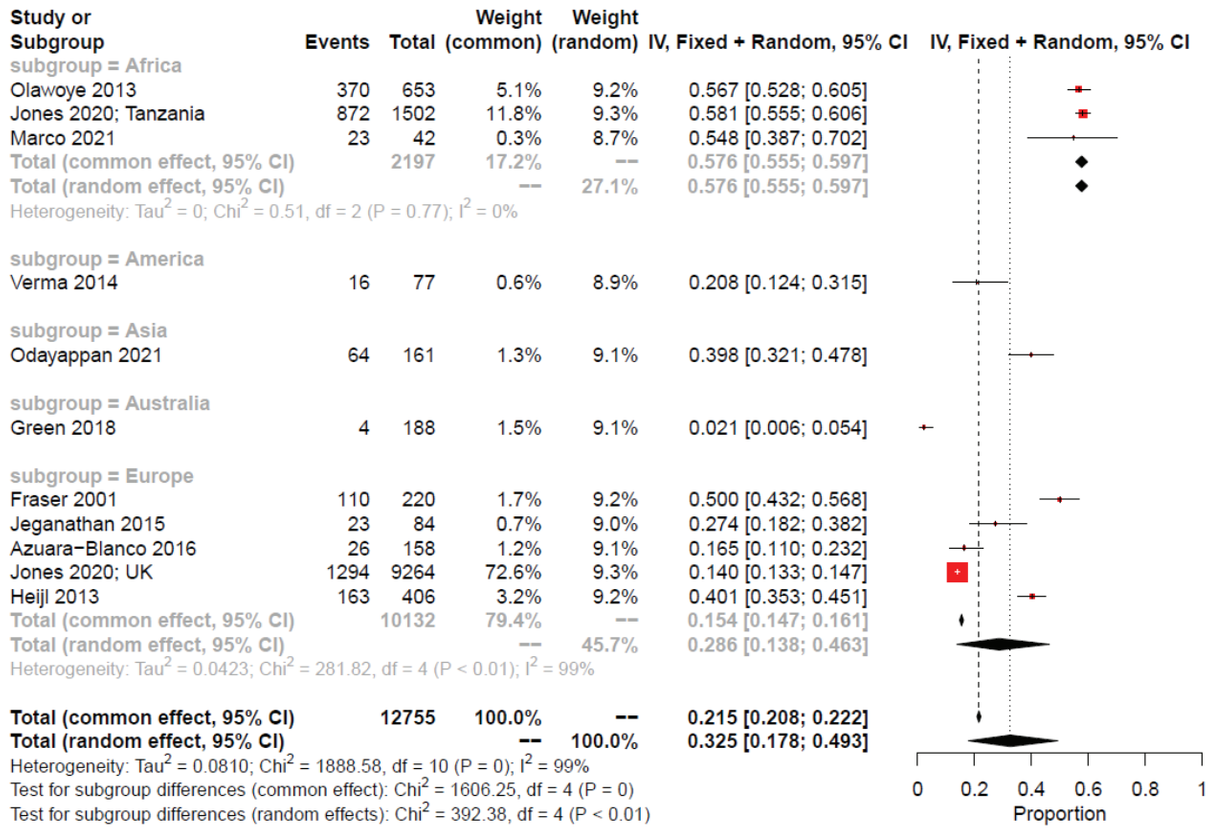



**Figure 6:** Results of subgroup analyses based on method of classification of advanced glaucoma (Humphrey Visual Field vs optic disc criteria)

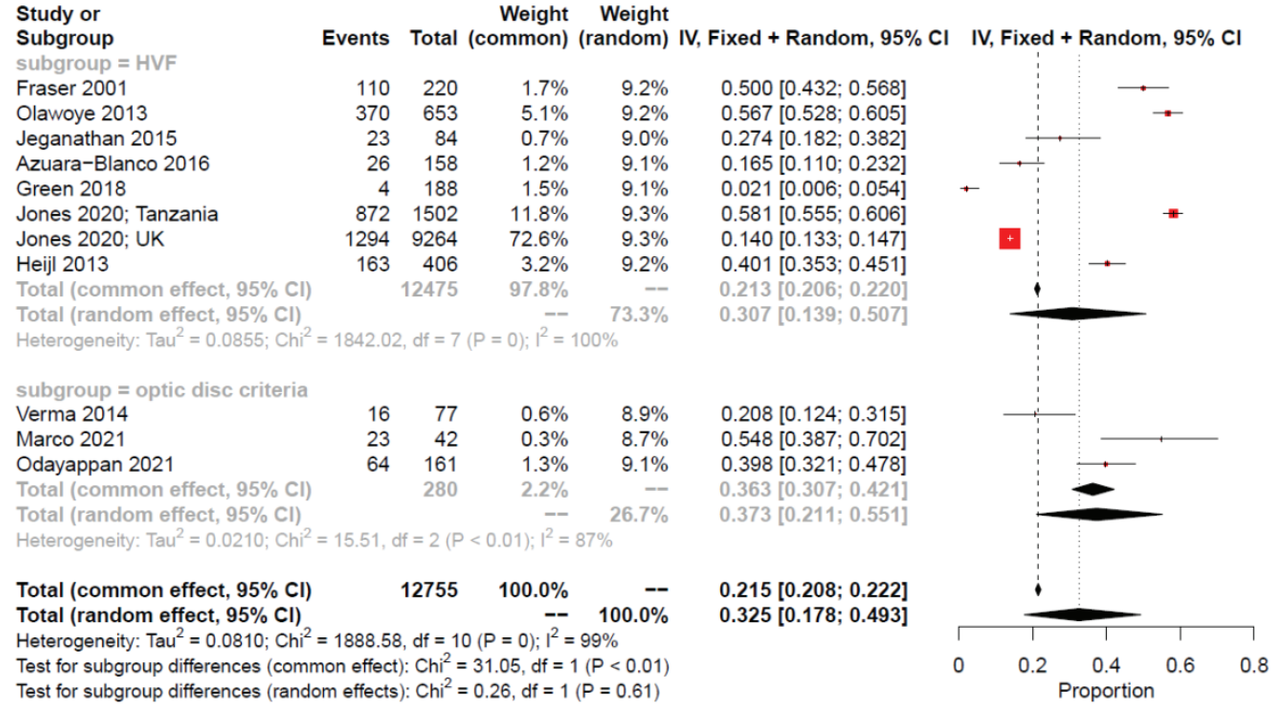
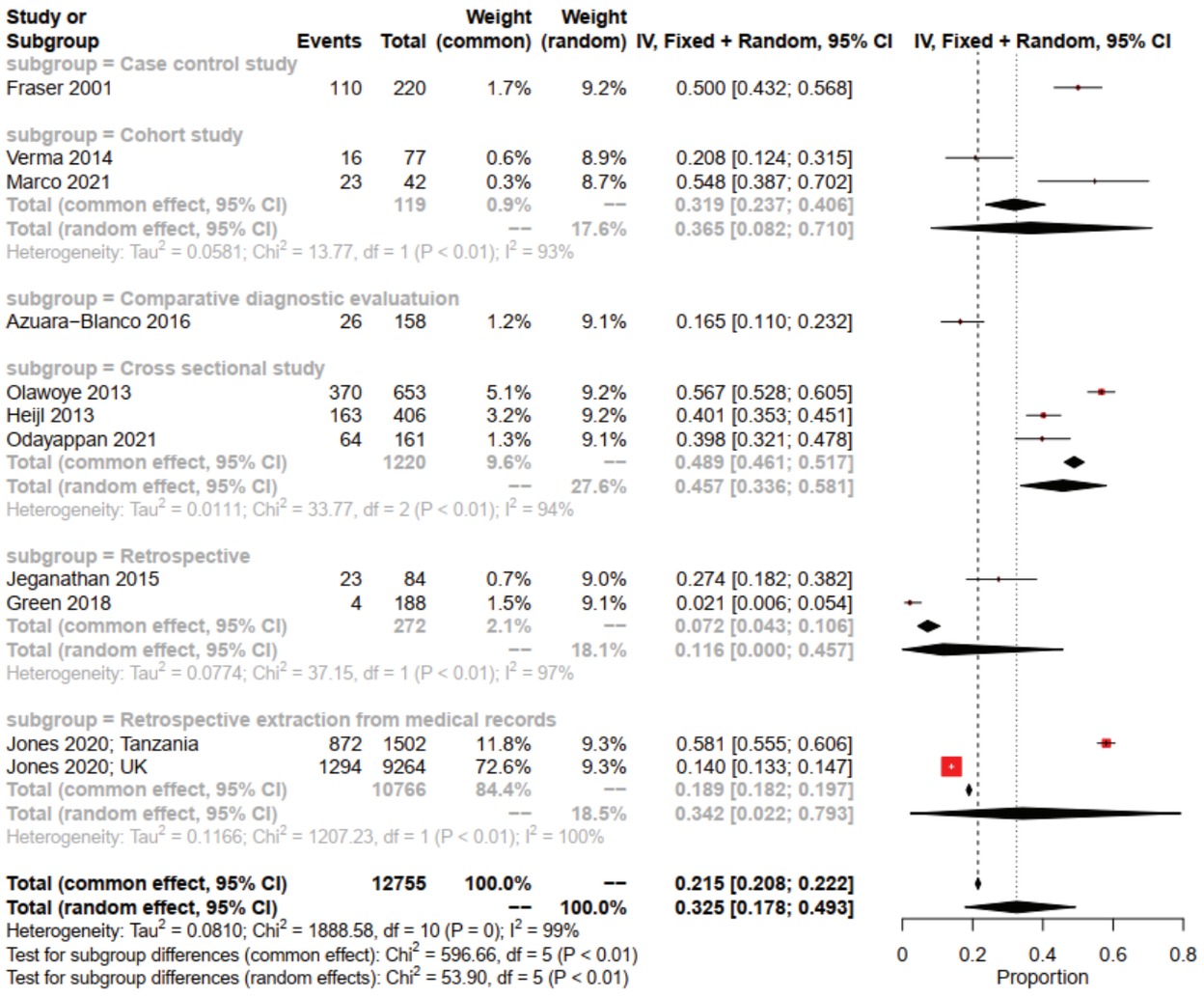


**Figure 7:** Results of subgroup analyses based on study design used




We performed a qualitative assessment of studies' quality. All studies were assigned quality of reporting as per the quality assessment tool used. However, no study was disqualified due to the technical quality.

## DISCUSSION

The pooled proportion of late presenting glaucoma patients was 0.325 (95% confidence interval 0.178-0.4931). From this study finding, this indicates that 32% of all referred newly diagnosed glaucoma patients are late presenters.

In our study we demonstrated equally a varied range of proportion of advanced glaucoma patients, from 2% to 58% as demonstrated earlier in the results. We however were interested in those patients having advanced glaucoma and presenting for the first time at the initial diagnosis centre, whom we referred to as late presenting patients. These patients had been referred to a tertiary eye centre for a definitive diagnosis and management.

Advanced glaucoma has been a topic of interest and various studies have estimated the incidence of advanced glaucoma. This varies from 10% to 61% depending on study location, study design and study participants[5,19,27]. Our study findings also fall within this range, but on the higher side since it indicates over three in ten glaucoma patients present late.

In the included studies, out of the late presenting patients, (n= 2,967), 2,883 of them had previous contact with a primary eye health worker. The proportion did not vary significantly among studies that were analysed. This indicates that usually an advanced glaucoma patient will have sought medical help upon noticing vision problems even prior to getting a definitive diagnosis.

*Referral by primary eye care workers:* Optometrists were noted as the primary eye health workers who had the most contact with the advanced glaucoma patients. This finding reflects that in most of the included studies, optometrists are the first point of contact with glaucoma patients.

The type of primary eye health worker who serves as the first contact for an advanced glaucoma patient varies from country to country or region to region depending on various health system unique set up. In England and most other western countries, most referrals to the hospital eye service originate from community optometrists, who have been demonstrated to have a particularly low threshold for glaucoma diagnosis[28,29]. This study finding could also be interpreted that patients usually interpret their visual problem as needing refractive attention rather than medical treatment.

The first point of contact for a patient largely determines the disease outcome. In African countries, and most other developing countries, patient referrals to a tertiary eye unit are done by a varied range of primary eye care workers.This varies from private facilities, government owned primary care facilities, traditional healers as well as local pharmacies[30,31]. The choice of facility to visit has been shown to largely depend on proximity and cost, with the low income group preferring the less costly primary health facilities. All these stakeholders should be sensitised and integrated to establish protocol and referral pathways for eye patients. From our included studies in developing countries, primary contact area was at a primary health facility.

*Geographical region:* When we analyse for geographical region, studies carried out in Africa had a higher percentage of late presenters as compared to the European population (57.6% in Africa vs 28.6% in European subgroup). The heterogeneity also dropped in the analysis of the African subgroup. This was however from only three studies. These findings could be due to the more streamlined health care system in developed countries that allows for early detection of glaucoma as well as timely referral of patients.

We compared two sets of similar studies conducted with reproducible methods, one retrospective study in Tanzania and UK done from data collected between 2009 to 2017 with 10,766 study participants while the other being cohort studies in Canada vs Kenya. Both demonstrate a higher incidence of late presenters in the less developed countries. The Tanzanian subset showed a proportion of 58.1 (55.6, 60.6) percent of late presenters, while in comparison a lower proportion in England of 14.0% (CI, 95%: 13.3, 14.7). Among other factors, the study identified fewer community based optometrist as a barrier for access to regular eye examinations in a vast and underserved geographical region. In addition, another challenge identified, despite presence of community optometrists was lacking engagement of the community to take up the existing eye services seeing as there was a significant proportion of glaucoma patients in UK still presenting late (14.7%).

Two cohort studies had a similar study design but in different geographical locations[20,23]. The Kenyan study[20], also showed a higher proportion of late presenters as compared to the Canadian group[23]. The Kenyan group showed 54.76% (23/42) of all glaucoma patients as late presenters as opposed to the Canadian group who had 20.78% (16/77) of all glaucoma patients being late presenters.

Africa has been shown to carry the most burden of disease from glaucoma in terms of visual disability as well as economic burden[32]. Residing far away from hospital has been demonstrated as a barrier to access of glaucoma services[6]. As much as primary eye care workers are needed in the low resource countries, their distribution should be equally proportionate in all regions to allow access by eye patients. All these efforts should be therefore directed toward reducing the number of late presenters in this region.

Future studies should consider comparing the characteristics of late presenting patients in the various macro-geographic continental regions, as in, Asia, Africa, Europe, north America, Latin America and the Caribbean, and Oceania in greater depth. Only one study was carried out in Asia[17].

Classification of advanced glaucoma: When we analysed for effect of studies that utilised Humphrey perimetry versus those that used optic disc signs only, we found that the latter group had a higher proportion of late presenters (37.3%), but with a lower heterogeneity.Three studies used the optic disc criteria for classification of advanced glaucoma.

Most of the studies that used perimetry had the same criteria for diagnosing advanced glaucoma by using the median deviation. Fraser[18] described late presenters, by visual field loss from fixation, this being a field loss within five degrees of fixation and greater than thirty degrees in one or both eyes. All these are however acceptable in the Hodapp, Parrish and Anderson's classification described earlier. This allowed for comparison of data between the study participants. Use of perimetry however could potentially have locked out from the study those subjects who could not be in a position to undertake or successfully complete the test.

*Study design:* Despite the study design employed, there was a high heterogeneity observed between the studies. This heterogeneity dropped, insignificantly, in the subgroup of cohort studies.

The quality of all studies was generally high, demonstrated low risk of bias, and satisfied the majority of the risk of bias and applicability criteria. The risk of bias from these studies was mostly from participant bias, which reflects the diversity in the methods of recruitment of patients to a particular study.

## Limitations

This systematic review as described by the included studies, doesn't accurately capture time before presentation. Glaucoma is a chronic progressive disease

and it would be helpful to know how far in the disease progression that most patients present so as to know when to intensify screening efforts. Additionally, Humphrey visual field testing is a subjective psychophysical testing method. It is therefore never completely accurate nor reproducible.

## CONCLUSIONS

We reviewed ten studies that reported the prevalence of late presenting glaucoma patients which was found to be 32.5% (95% CI 0.178 -0.493). Out of these patients, we found a large proportion of them, 96% (95% CI 0.85-1.00), had previous contact with a primary eye health worker before getting a definite diagnosis in a tertiary eye hospital.

This study demonstrates the value of primary eye care workers bridging the gap between glaucoma patients and prevention of blindness from glaucoma. This finding therefore demonstrates a huge opportunity to channel efforts and resources toward investing in primary eye health workforce for referral of glaucoma patients and subsequently preventing irreversible blindness.

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*Availability of data and materials:* The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

*Competing interests:* The authors declare that they have no competing interests.

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Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42022324514.

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