AOSIS

Identifying the critical factors that influence intraocular pressure using an automated regression tree

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Background: Assessment of intraocular pressure (IOP) is an important test in glaucoma. In addition, anterior segment variables may be useful in screening for glaucoma risk. Studies have investigated the associations between IOP and anterior segment variables using traditional statistical methods. The classification and regression tree (CART) method provides another dimension to detect important variables in a relationship automatically.

Aim: To identify the critical factors that influence IOP using a regression tree.

Methods: A quantitative cross-sectional research design was used. Anterior segment variables were measured in 700 participants using the iVue100 optical coherence tomographer, Oculus Keratograph and Nidek US-500 ultrasonographer. A Goldmann applanation tonometer was used to measure IOP. Data from only the right eyes were analysed because of high levels of interocular symmetry. A regression tree model was generated with the CART method and Pearson's correlation coefficients were used to assess the relationships between the ocular variables.

Results: The mean IOP for the entire sample was 14.63 mmHg ± 2.40 mmHg. The CART method selected three anterior segment variables in the regression tree model. Central corneal thickness was the most important variable with a cut-off value of 527 μm. The other important variables included average paracentral corneal thickness and axial anterior chamber depth. Corneal thickness measurements increased towards the periphery and were significantly correlated with IOP ($r \geq 0.50$, $p \leq 0.001$).

Conclusion: The CART method identified the anterior segment variables that influenced IOP. Understanding the relationship between IOP and anterior segment variables may help to clinically identify patients with ocular risk factors associated with elevated IOPs.

Introduction

Glaucoma is an optic neuropathy that sometimes results in irreversible blindness.[1] After cataracts, glaucoma is the second most prevalent cause of global blindness,[2] and it is estimated that almost 80 million people worldwide will be affected by this optic neuropathy by the year 2020.[3] Because of the high prevalence of this ocular disease, the economic and social implications of glaucoma have been outlined in recent studies.[4,5] In Africa, primary open-angle glaucoma (POAG) is more prevalent than primary-angle closure glaucoma, and over the next 4 years, the prevalence of POAG in Africa is projected to increase by 23% corresponding to an increase from 6.2 million to 8.0 million affected individuals.[3] Consequently, in Africa, there have been recommendations to incorporate glaucoma screening procedures into routine eye examinations as well as implement glaucoma blindness control programs.[6,7]

The assessment of intraocular pressure (IOP) is a fundamental clinical test used for the screening, diagnosis and management of glaucoma.[1,8] IOP is still considered as an important risk factor for glaucoma,[1,9] but previous studies have reported that other ocular anterior segment variables are also useful in screening for individuals at risk for glaucoma.[10,11,12,13] For example, the Ocular Hypertension Treatment Study highlighted the importance of central corneal thickness (CCT) in evaluating risk for POAG.[10] Some studies have indicated that other anterior chamber variables (such as depth and angle width) may be useful for evaluating risk for developing angle closure glaucoma.[12,13,14] As a result, the relationship between IOP and anterior segment ocular variables has been investigated in both population-based[15,16,17] and clinic-based[18,19,20] studies.

Investigating the relationship between IOP and anterior segment ocular variables may be useful for better understanding the association between these ocular variables and IOP.[8] This knowledge may help to clinically identify patients with ocular risk factors associated with elevated IOPs.[21] The association between IOP and CCT is well known with several studies[22,23,24] noting higher IOP measurements in eyes with thicker CCT measurements. In contrast, the literature related to IOP and corneal curvature is inconsistent, with some studies[20,25] reporting no association while other studies[15,16,19,21,26] reported significantly higher IOPs in eyes with steeper corneal curvatures. No associations have been found between IOP and corneal diameter[27] or anterior chamber angle (ACA) variables.[15,28,29]

The majority of the studies have used traditional statistical methods, such as correlation and regression analyses, to assess the relationship between IOP and anterior segment ocular variables.[15,16,17,19] However, these statistical methods may result in erroneous conclusions especially when their inherent assumptions are misunderstood and/or results are inaccurately interpreted.[30,31] In addition, both correlation and linear regression analyses only show linear relationships and may omit the more complex relationships that exist when you have more than two variables.[32,33] Not surprisingly therefore, several researchers have cautioned against misinterpreting a large significant correlation between two variables as a causal relationship between the two variables of interest.[30,32,33]

In the absence of any ocular abnormalities, ocular variables for the right and left eye of the same individual are related.[34,35] Furthermore, the different ocular variables, within the same eye, may be inherently related and correlated. The related nature of clinical variables, from a particular biological system, is not exclusive to optometry and has also been shown in dental and medical research.[31,36] Multiple regression analysis is often used to make predictions and suggest explanations for a dependent variable when there are more than two independent variables.[36] When clinical variables, which are used in multiple regression analysis, are highly correlated, it results in mathematical coupling and collinearity.[36,37] Collinearity can distort the relationship between two ocular variables especially when both variables of interest are highly correlated with another ocular variable.[30] Therefore, a statistical method that overcomes some of these challenges is preferred for assessing the relationship between IOP and multiple anterior segment ocular variables.

Classification and regression tree (CART) is an analysis method that is able to detect which variables are important in a relationship or model.[38,39] This method is useful for large data sets that contain multiple variables that may have non-linear relationships.[40,41] The CART method has several advantages including that it can be used with skewed data, requires minimal input from the researcher because of an automatic independent variable selection process, is able to handle collinearity together with missing variables and displays information in a way that is simple to interpret even for individuals with limited statistical backgrounds.[41,42,43]

The CART method generates a regression tree model when a dependent variable is predicted based on multiple independent variables.[44] In a regression tree model, the dependent variable is continuous while the independent variables may be either continuous or categorical.[41,43] Furthermore, regression tree models are simple to present and resemble the process used in clinical reasoning as they are generated based on a logical sequence of 'if-then' statements or decision rules.[44] For this reason, the CART method is said to have greater practical relevance in clinical situations.[42] To this end, several studies have produced regression trees, using the CART method, for clinical conditions including myocardial infarction,[45] dental caries,[46] asthma,[47] dry eye,[48] keratoconus[49] and low vision rehabilitation.[50]

Graphically, regression tree models consist of a single node (call the root) and consecutive internal nodes that are defined by a characteristic-independent variable and its respective cut-off value that splits the data into two sub-groups.[40,41,42] At each internal node, the CART method iteratively evaluates all the independent variables and automatically selects the variable and its cut-off value that is most efficient in splitting the data into two sub-groups containing similar values for the dependent variable.[41,43,51] Consequently, regression tree models are generated using binary recursive partitioning because of the two-way split at each internal node.[42,44] The process of splitting the sub-groups is continued until the data cannot be split any further resulting in terminal nodes.[40] The root node contains all cases in the data while each terminal node depicts the number of cases (from the data) and the mean value of the dependent variable located within that branch.[40]

Regression tree models that consist of too many branches are unnecessarily large and complex.[40] Such a model is likely to 'overfit' the data resulting in poor generalisability to new data.[40,42,49] Thus, a pruning process is applied to the initial large regression tree model, which removes internal nodes that are considered 'noise' and contribute no predictive power to the regression tree model.[51] Consequently, pruning often results in a smaller regression tree model.[40] Furthermore, pruned regression trees have better predictive accuracy because they go through a cross-validation procedure to select the optimal-sized tree.[43]

The aim of this study was to identify the critical anterior segment ocular variables that influence IOP using an automated regression tree. By using the CART method, it is hoped that the statistical analysis would validate which anterior segment variables have the most influence on IOP. In this way, the CART method may also suggest mechanisms of anterior segment variables affecting IOP that may not have been investigated previously.

Methodology

The study employed a quantitative cross-sectional research design and was conducted at the University of KwaZulu-Natal eye clinic. The study population consisted of black

and Indian students from the University of KwaZulu-Natal. Two-stage random sampling was used to recruit 700 (350 black and 350 Indian) participants aged between 17 and 30 years. Participants were tested using screening procedures to determine their eligibility in accordance with the study inclusion criteria. The screening procedures included case history (ocular and medical), logarithm of the minimum angle of resolution (LogMAR) distance visual acuity, autorefraction (using the Nidek AR-1) and subjective refraction, slit-lamp biomicroscopy, ophthalmoscopy and non-contact tonometry (via the Nidek NT530P). Participants were excluded with visual acuity (unaided or best corrected) worse than 0 LogMAR, IOP greater than 21 mmHg, contact lens wear in the past 3 weeks or previous history of ocular trauma and/or surgery, systemic and/or ocular diseases and currently on medication. Thereafter, data collection procedures were performed on eligible participants.

Corneal thickness and ACA variables such as the angle-opening distance taken at 500 μm (AOD500) and trabecular-iris angle (TIA) were scanned and measured using the Optovue iVue100 optical coherence tomographer (OCT). This Fourier-domain OCT is capable of generating 25 000 A-scans per second with an axial and transverse resolution of 5 μm and 15 μm, respectively.[52] A pre-programmed algorithm in the iVue100 OCT defines the corneal epithelium and endothelium as the anterior and posterior boundaries, respectively.[52] The corneal thickness is automatically

determined as the distance between these two boundaries. The AOD500 and TIA were measured using the inbuilt angle tools in the iVue100 OCT. As per the manufacturer's recommendations,[52] repeat scans were taken when the scan was labelled as poor on the laptop screen or had a scan quality index of < 27. During scanning, the real-time images of the participant's eye with either the cornea or ACA were monitored on the laptop screen.

The corneal pachymetry scan protocol which consists of eight radial (6 mm) line scans of 1024 A-scans each was used to measure corneal thickness.[52] During corneal scanning, participants were instructed to look at the internal fixation target. The corneal pachymetry scan protocol displays the average corneal thickness in a 6 mm × 6 mm pachymetry map (Figure 1). This pachymetry map (Figure 1) is divided by rings into three corneal sections (central, paracentral and peripheral). CCT is defined as the average thickness in the central 2-mm ring. The middle and outermost rings, of 5-mm and 6-mm diameter, denote the paracentral and peripheral corneal sections, respectively. The paracentral and peripheral cornea are further divided into eight zones (superior, superior-temporal, temporal, inferior-temporal, inferior, inferior-nasal, nasal and superior-nasal). The average thickness in the central, paracentral and peripheral corneal sections (17 zones) are displayed in the corneal pachymetry map using a false-colour display (Figure 1). In this study, the average paracentral corneal thickness (ParaCT) and average
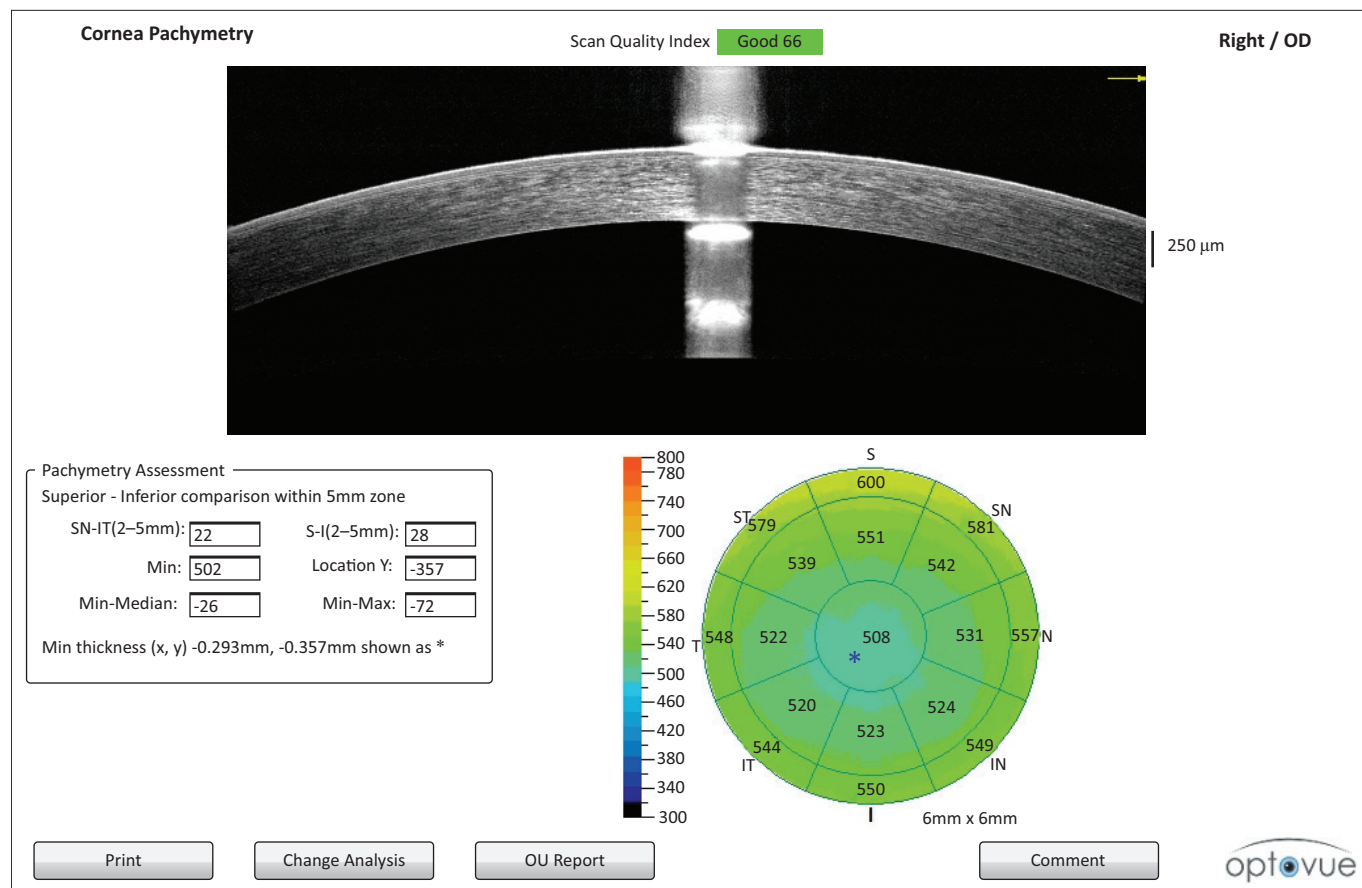

FIGURE 1: Corneal pachymetry map showing the mean corneal thickness in the centre and each zone in the paracentral and peripheral cornea.

peripheral corneal thickness (PeriCT) were computed as the average of the eight zones therein.

The cornea angle scan protocol was used to image and measure the ACA variables (AOD500 and TIA). The cornea angle scan consists of a single (5 mm) line scan of 1024 A-scans.[52] The ACAs in the horizontal meridian (nasal and temporal) were measured as they are unlikely to be distorted by the eyelids[53] and have better repeatability than ACAs in the vertical meridian.[54] During cornea angle scanning, participants were instructed to look at the inbuilt external fixation target mounted on the side of the iVue100 OCT while the line scan was centred on the limbus (nasal or temporal). This ensured that the limbal surface was aligned to the OCT light beam and that the cornea appeared flattened to minimise diffraction and distortion.[53,55] The cornea angle scan protocol displays the ACA analysis using a gray-scale display (Figure 2).

The ACA variables (AOD500 and TIA) were determined using the method described by Pavlin et al.[56] and subsequently used in several other studies.[28,57,58] This method involved identifying ACA landmarks including the angle recess, scleral spur, point on the trabecular meshwork 500 μm anterior to the scleral spur and the corresponding perpendicular point on the iris surface.[55,59] The AOD500 represents the linear distance (in μm) from the point on the trabecular meshwork to the perpendicular point on the iris surface[55] (Figure 2). In this study, the average AOD500 was

computed as the average of the nasal and temporal AOD500 measurements. The TIA represents the angular measurement (in degrees) of the triangle formed by the angle recess, point on the trabecular meshwork and the perpendicular point on the iris surface[55] (Figure 2). In this study, the average TIA was computed as the average of the nasal and temporal TIA measurements.

Previous studies have reported that OCT devices have good repeatability and reproducibility for measuring corneal thickness[60,61] and ACA variables.[59,62] Because the ACA variables (AOD500 and TIA) were measured manually, the researcher re-measured the ACA variables on 10 randomly selected participants after data collection. The re-measured ACA measurements showed good agreement with the original measurements (intraclass correlation coefficients $\geq$ 0.965). Corneal curvature and diameter were measured using the Oculus Keratograph, which is considered reliable and has been used in previous studies.[63,64] Anterior chamber depth (ACD) was assessed using the Nidek US-500 A-scan ultrasound device, which has been used in previous studies to measure axial biometry.[65] The IOP was measured with a Goldmann applanation tonometer, which is regarded as the gold standard for measuring IOP.[66] To promote standardisation, all measurements were performed by one researcher and three measurements per variable were recorded and averages computed.
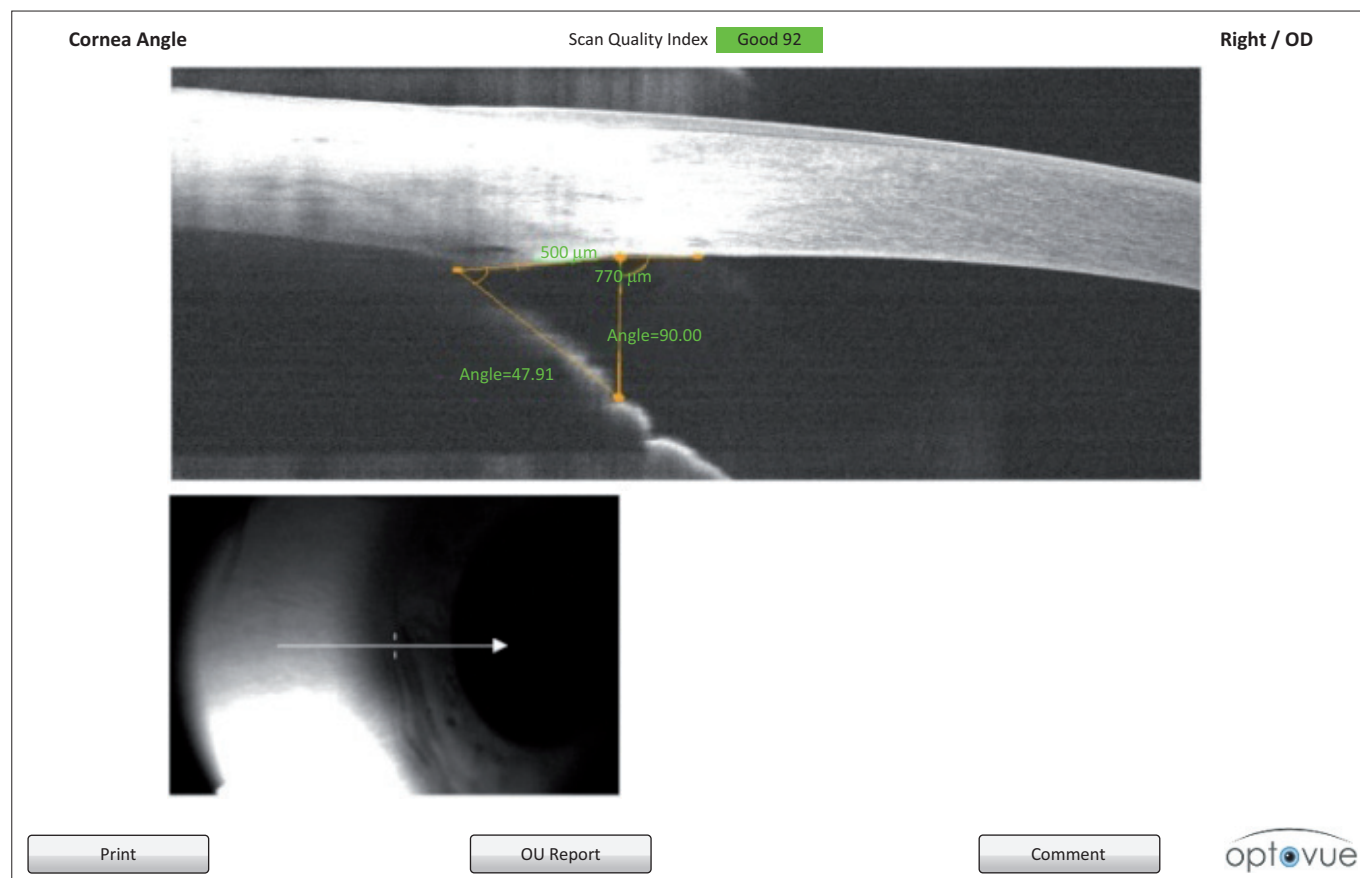

FIGURE 2: Cornea angle analysis showing the ACA variables (AOD500 and TIA).

Data were captured and analysed with two software packages namely the Statistical Package for Social Sciences and the R Package. The Shapiro–Wilk's test and graphical inspection of histograms were used to assess the distributions of the data concerned. Descriptive statistics included means and standard deviations. Interocular symmetry and the reproducibility of ACA measurements were assessed using intraclass correlation coefficients.[35] Dependent-sample t-tests were used to assess differences in corneal thickness measurements in the different corneal sections. Pearson's correlation coefficient was used to assess the relationship between study variables. The RPART function in the R Package was used to generate the regression tree models. Eleven independent variables were entered into the CART method including three demographic covariates (gender, age and race) and eight anterior segment ocular variables (CCT, average ParaCT, average PeriCT, corneal diameter, average corneal curvature, axial ACD, average AOD500 and average TIA). The study adopted a 95% significance level where $p \leq 0.05$ were considered statistically significant.

Ethical considerations

Ethical approval for the study (reference number BE 189/12) was obtained from the Biomedical Research and Ethics Committee of the University of KwaZulu-Natal. All participants provided written informed consent after a discussion of the nature of the study procedures involved. All ethical guidelines, in accordance with the Declaration of Helsinki, were adhered to during the study.

Results

The study sample included 700 participants with an equal distribution of male ($n = 350$) and female ($n = 350$) participants. Furthermore, 50% of the sample consisted of South African blacks and the other 50% were South African Indians. The participants' ages ranged between 17 and 29 years, with a mean of 20.42 ± 1.80 years. The preliminary analysis showed that anterior segment ocular variables of the right and left eyes were similar (intraclass correlation coefficients ≥ 0.880). The IOP measurements of the right and left eye were also similar with a mean difference of only 0.27 mmHg and intraclass correlation coefficient of 0.884. Therefore, data from only the right eyes of the 700 participants were analysed because of the high levels of interocular symmetry.

Table 1 shows the ocular characteristics of the study participants. The mean IOP for the entire sample was 14.63 mmHg ± 2.40 mmHg (range, 10 mmHg – 21 mmHg). The CCT was significantly thinner than both the average ParaCT (mean difference of 19.15 μm, $p \leq 0.001$) and average PeriCT (mean difference of 44.91 μm, $p \leq 0.001$). The IOP was significantly correlated ($r \geq 0.50$, $p \leq 0.001$) with corneal thickness measurements in all three sections (central, paracentral and peripheral). Even though IOP was significantly correlated with corneal diameter, axial ACD and average AOD500, the correlation coefficients noted were weak ($r \leq 0.15$, $p \leq 0.016$). There was no association between IOP and average corneal curvature ($p = 0.689$) or TIA ($p = 0.858$).

TABLE 1: Means and standard deviations for ocular characteristics.

| Characteristic	Mean ± s.d.
IOP (mmHg)	14.63 ± 2.40
CCT (μm)	501.91 ± 33.74
Average ParaCT (μm)	521.06 ± 34.56
Average PeriCT (μm)	546.82 ± 35.71
Corneal diameter (mm)	11.95 ± 0.42
Average corneal curvature (D)	43.19 ± 1.54
Axial ACD (mm)	3.43 ± 0.24
Average AOD500 (μm)	552.51 ± 110.68
Average TIA (°)	36.68 ± 4.65

IOP, intraocular pressure; CCT, central corneal thickness; ACD, Anterior chamber depth; AOD500, Angle-opening distance taken at 500 μm; TIA, trabecular-iris angle; s.d., standard deviation.
n = 700.

The unpruned and pruned regression tree models, with the decision rules, generated automatically by the CART method are shown in Figures 3 and 4, respectively. The first box in both regression tree models (Figures 3 and 4) is the root node which contains all cases ($n = 700$) and displays the mean dependent variable (IOP = 14.63 mmHg). The successive boxes in grey show the internal nodes which contain the different independent variables and their respective cut-off values. Each independent variable occupies a level with level one being more important than level two and so on. If the condition (independent variable and its respective cut-off value) is satisfied, the tree is followed along the left branch (shown as YES in the regression tree models). However, if the condition is not satisfied, the tree is followed along the right branch (shown as NO in the regression tree models).

Only 4 of the 11 independent variables were selected for inclusion in the unpruned regression tree model. The selected variables were, in order of decreasing importance, CCT, PeriCT, axial ACD and ParaCT (Figure 3). Cross-validation was then used to prune this regression tree model to automatically generate an optimal-sized regression tree. The pruned regression tree model consisted of only three independent variables (CCT, PeriCT and axial ACD) omitting the ParaCT from the unpruned tree (Figure 3). There were 7 and 5 terminal branches in the unpruned and pruned regression tree models, respectively (Figures 3 and 4). In addition, any further splitting of the data set did not show any significant improvement in the regression tree model.

In both regression tree models (Figures 3 and 4), CCT was the most important independent variable with a cut-off value of 527 μm as identified at level one. At level two, the PeriCT was identified as the next most important variable with cut-off values of 527 μm and 625 μm for CCT values that were < 527 μm and ≥ 527 μm, respectively. In participants with CCT ≥ 527 μm and PeriCT < 625 μm, the predicted IOP differed by ~1.25 mmHg depending on whether the axial ACD (level three) was < 3.58 mm or ≥ 3.58 mm. The highest IOP (19.36 mmHg) was found in 11 participants who had CCT ≥ 527 μm and PeriCT ≥ 625 μm. In the unpruned regression tree model (Figure 3), the lowest predicted IOP of 12.85 mmHg was noted in participants ($n = 119$) with CCT and PeriCT < 527 μm together with ParaCT < 488 μm. In the
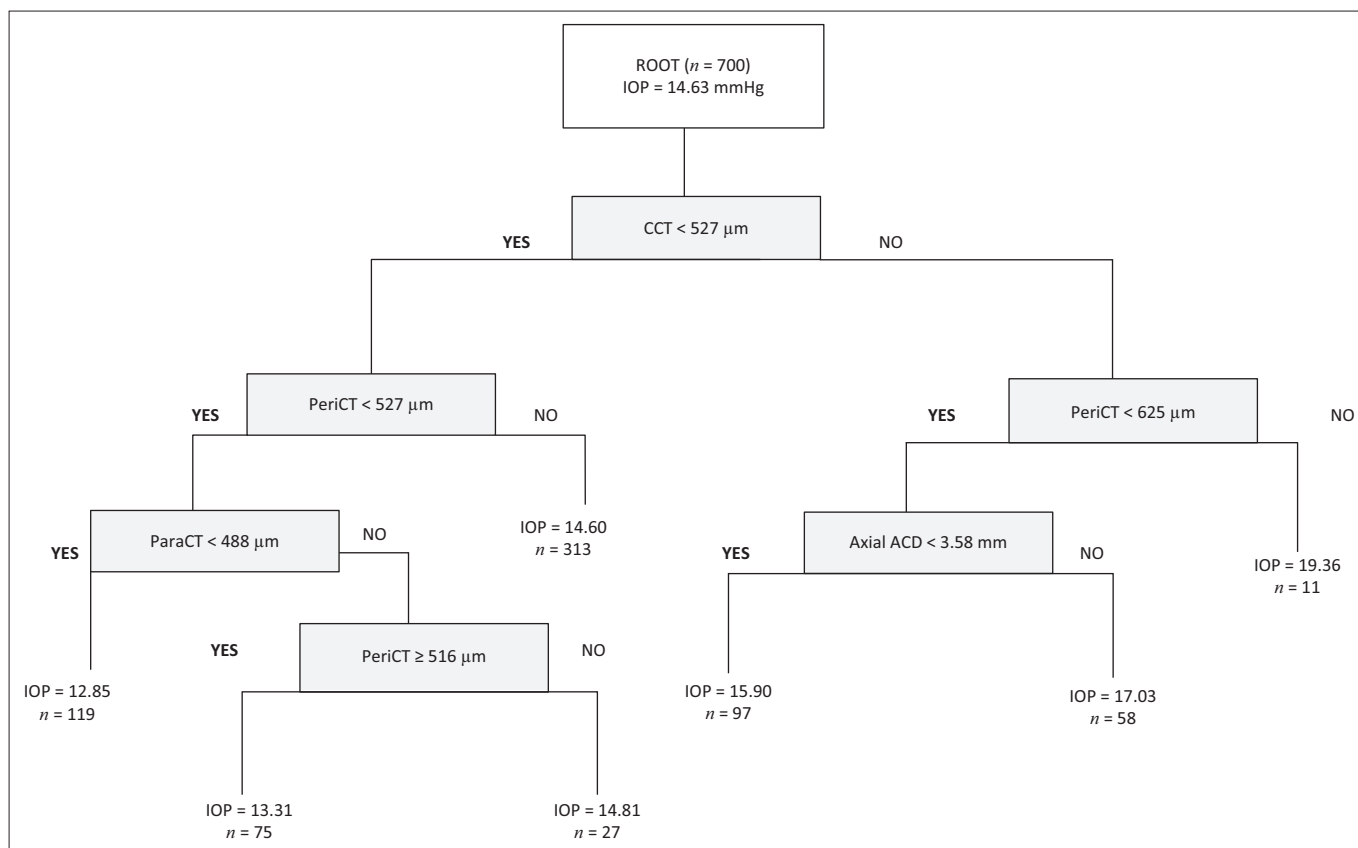
IOP, intraocular pressure; CCT, central corneal thickness; ACD, Anterior chamber depth.
FIGURE 3: Unpruned regression tree model, automatically generated by the classification and regression tree method, for prediction of intraocular pressure.
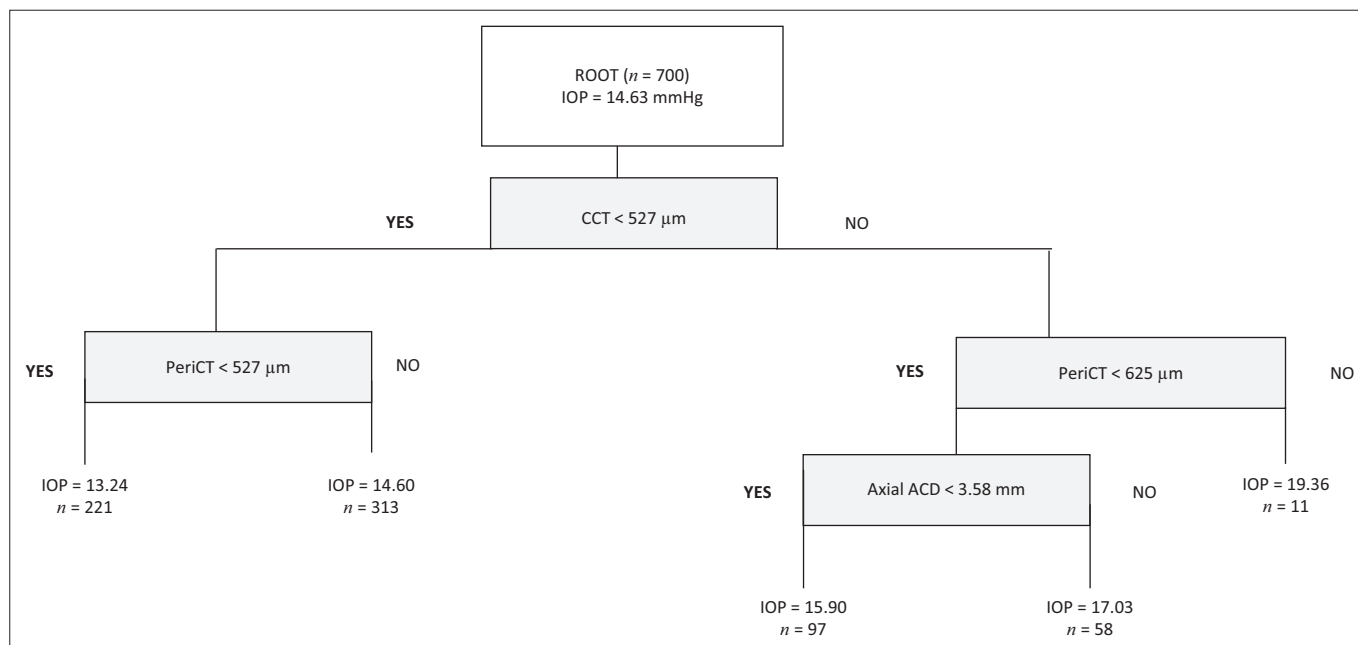
IOP, intraocular pressure; CCT, central corneal thickness; ACD, Anterior chamber depth.
FIGURE 4: Pruned regression tree model, automatically generated by the classification and regression tree method, for prediction of intraocular pressure.

pruned regression tree model (Figure 4), the majority of participants (n = 534) had CCT < 527 μm and IOP measurements < 15 mmHg. The IOP was 13.24 mmHg in 221 participants with both CCT and PeriCT < 527 μm. The IOP was 14.60 mmHg in 313 participants who had CCT < 527 μm but PeriCT ≥ 527 μm.

Discussion

The aim of this study was to identify which anterior segment ocular variables significantly influence IOP. Instead of solely using traditional statistical methods that require an a priori deliberate selection of which variables to analyse, from the

researcher and/or statistician, the CART method was also used. This method is often used in data mining, makes no assumptions about the data and automatically selects the most important variables in a relationship or model.[38,39] The results showed that four anterior segment variables influenced IOP. Three of these variables were measures of corneal thickness (CCT, PeriCT and ParaCT) while the other was the axial ACD.

Both regression tree models showed that CCT (at level one) was the most important anterior segment ocular variable that influenced IOP. This is not surprising as several studies have reported strong associations between IOP and CCT in normal individuals[22,23,24] and individuals with glaucoma.[67] Even though such associations have been reported consistently in the literature, the exact reason for this association is unclear. However, it could be a consequence of both IOP and CCT being measured at the corneal optical zone and the characteristics therein. For example, the corneal optical zone, which has a diameter of 4 mm, is thought to have a uniform spherical curvature.[68] A regular corneal surface is important because applanation tonometry measurements are estimated based on the force needed to applanate a certain area.[69]

A fixed area of flattening is especially important for Goldmann applanation tonometry because, at an applanation diameter of 3.06 mm, the opposing effects of corneal rigidity and the surface tension of the tear film are cancelled out.[69] Furthermore, the corneal optical zone has reduced thickness,[70,71] is more compact and has lower mean collagen inter-fibrillar separations[72] compared to the corneal periphery. These differences between the corneal optical zone and periphery could account for differences in resistance to applanation tonometry.[73] It is speculated that these anatomical, physiological and topographical differences may also account for the association between IOP and CCT at the corneal optical zone. This explanation is reasonable because it has been shown that corneal biomechanical properties influence IOP.[19,74] Furthermore, in this study the IOP measurements in the root node were split based on cut-off CCT value of 527 μm, which is similar to the theoretical calibrated CCT measurement (520 μm) for Goldmann applanation tonometry.[75]

After CCT, the next important anterior segment variables were PeriCT, ParaCT and axial ACD. Corneal thickness beyond the central optical zone is not routinely measured in clinical practice. However, the results suggest that these corneal thicknesses may be important determinants of IOP. No studies could be found that investigated the relationship of IOP and corneal thickness measurements beyond the central optical zone (peripheral corneal thickness). The paucity of literature regarding IOP together with peripheral corneal thicknesses may relate to the fact that IOP is also not usually measured beyond the corneal optical zone. However, such measurements may be useful estimates of IOP, especially in instances of refractive surgeries, central corneal ulcers, epithelial oedema and high irregular astigmatism.[73,76] Moreover, studies conducted on IOP measured at points beyond the corneal optical zone have reported reliable IOPs that are in agreement with IOPs measured at the central optical zone.[73,76] The exact reason for the influence of peripheral corneal thicknesses on IOP is not readily explained. However, it may not be related to the thinnest corneal point being located at the corneal apex, as previously thought, but rather in the infero-temporal cornea.[70,77] It is also likely that corneal rigidity will vary in relation to the different corneal thickness profiles and may also influence IOP.[19,74]

In this study, the mean CCT recorded with the iVue100 OCT was ~502 μm. Previous studies[78,79] involving young South African adult samples, with similar demographic characteristics, have reported mean CCT measurements of ~519 μm. Thus, mean CCT in this study was thinner when compared with other studies involving similar South African samples. This finding may be accounted for by using different instruments to measure CCT because this study used a device based on optical coherence tomography while previous studies[78,79] used devices based on Scheimpflug photography. The overestimation of CCT measurements by Scheimpflug photography devices compared with optical coherence tomography devices have also been reported when CCT measurements were compared on the same study sample.[71] The mean CCT in this study is also lower than the normal expected CCT measurement of 535 μm reported by Doughty and Zaman[80] in their meta-analysis. Thus, possible factors that may explain this discrepancy include differences in study design, instrumentation, sample size and ethnicity.[80,81]

The normal axial ACD is about 3 mm with a wide range of 2.6 mm – 4.6 mm.[82] In this study, the mean axial ACD (3.43 mm) and axial ACD cut-off value (3.58 mm) in the regression tree models were within this expected range. Surprisingly, participants with axial ACDs deeper than the cut-off value had slightly higher IOPs (~1.25 mmHg). Tomoyose et al.[15] theorised that higher IOPs may not necessarily be associated with narrow anterior chambers when the ACA is open in normal individuals. In this study, axial ACD was selected as one of the important anterior segment ocular variables that influenced IOP. This finding is in contrast to previous studies,[15,26] which report no association between IOP and ACD. This difference may be due to a cohort effect because studies that noted no association between IOP and ACD consisted of primarily older Japanese participants.[15,26] It should be noted that Tomoyose et al.[15] reported on axial ACD, while Kawase et al.[26] reported on limbal ACD measurements.

In this study, the average AOD500 was 552.51 μm, which is similar to the calculated average AOD500 measurements by Cheon et al.[83] (555.50 μm) and Leung et al.[84] (549.50 μm). The average TIA was 36.68°, which is comparable with the mean TIA of 35.90° reported in a sample of young German adults (mean age of 32.1 years) by Müller et al.[55] when evaluated with another spectral-domain OCT. Despite also using a young adult sample (mean age of 25.93 years), Hosseini et al.[85] reported slightly higher mean TIA measurements (39.36°) when assessed with a Scheimpflug photography device.

In this study, no ACA variables were selected by the CART model to influence IOP. Furthermore, IOP was not associated with average TIA, whereas there was only a weak association with average AOD500 ($r = 0.09$; $p = 0.016$). These results are in agreement with previous studies that also reported no meaningful association in normal non-glaucomatous eyes between IOP and ACA variables.[28,29] However, other studies[17,21] that used gonioscopy to evaluate ACA width have reported that IOP and ACA width are related. Although both these studies further commented that the associations found were marginal[21] and would only result in small changes in IOP (0.2 mmHg for every 10° change in ACA width).[17]

In this study, other corneal variables (excluding CCT which has been discussed above) have revealed interesting results regarding their relations with CCT, roles in the CART analysis and associations with IOP. Consistent with previous studies,[70,71,77] corneal thickness increased significantly from the corneal centre towards the periphery. It is speculated that the normal thickening of the cornea towards the periphery is because of the increase in stromal collagen fibrils in the corneal periphery compared with the centre.[86] Both corneal curvature and diameter were not selected by the CART method for inclusion in the regression tree models. This finding is consistent with the lack of strong associations seen between IOP and corneal curvature or diameter as has been reported in other studies.[20,25,27]

Despite an equal distribution of male and female participants in the study sample, gender was not detected as an important factor in the regression tree models. This finding is consistent with some studies that also reported that IOP is not affected by gender.[8,18] Contradictory findings have been reported regarding IOP and age. Studies involving Asian individuals reported that IOP decreases with increasing age,[15,16,26] whereas other studies reported that IOP increases with increasing age.[8,87] In this study, IOP was not affected by age, which may be attributed to the small range of participants' ages in this study in contrast to other studies that reported associations between IOP and age.[8,26,87]

The mean IOP in the general population ranges between 11 mmHg and 21 mmHg.[1] The mean IOP of 14.63 mmHg in this study is almost identical to that reported by Sardiwalla et al.[78] Despite using a non-contact tonometer, Sardiwalla et al.[78] also measured IOP in a young South African adult sample and reported a mean IOP of 14.6 mmHg ± 2.80 mmHg. In contrast, the mean IOPs reported in several older South African samples[88,89] were smaller (13.7 mmHg – 13.9 mmHg) than those found in this study, which may be attributed to the influence of age on IOP.[15] This difference may also be related to differences in sample sizes wherein the studies with lower mean IOP measurements[88,89] consisted of larger study samples. Because this study only included participants with IOPs ≤ 21 mmHg, all sub-groups of participants shown in the terminal nodes of the regression tree models (Figures 3 and 4) can be considered as variations of an essentially normal young South African adult

population, although some eyes with IOP ≤ 21 mmHg could have normal-tension or low-tension glaucoma. However, the age range in this study (17–30 years) probably excluded such instances. From the regression tree models, it can be seen that based on some anterior segment ocular variables, there is a wide range of normal IOP (12.85 mmHg – 19.36 mmHg) in this young South African adult population.

Strengths of this study include the use of young South African adults consisting of an equal gender distribution with normal IOPs (≤ 21 mmHg) and standardised data collection examination protocols. A Fourier-domain OCT was used in conjunction with inbuilt fixation targets to minimise measurement errors associated with off-centre fixation. In addition, this study used an interesting multivariate statistical method to determine which anterior segment variables significantly influenced IOP. Even though the CART method is able to split the data by only one independent variable at a time,[41,43] this method still allowed the regression tree models to grow to 4 and 3 levels in the unpruned and pruned regression trees, respectively.

Possible limitations of this study include the narrow age range of participants and inclusion of participants with apparently normal IOP. This implies that the results of this study may not be generalised to older or younger South African individuals and those with IOP anomalies. Therefore, it is recommended that future studies include individuals with a wider age range and individuals with IOP anomalies to confirm if the same anterior segment variables influence IOP in such cases. Lastly, it is possible that other ocular variables and perhaps those of the posterior ocular segment such as posterior scleral rigidity and retinal nerve fibre layer thickness as well as axial length and refractive error might also influence IOP. Thus, it is recommended that future studies investigate the influence of posterior segment variables on IOP using the CART method as this may lead to an enhanced understanding of which ocular variables and their respective cut-off values influence IOP.

Conclusion

In this study an alternate way of evaluating the influence of anterior segment ocular variables on IOP is presented. Because IOP is an important consideration for glaucoma, understanding the relationship between anterior segment variables and IOP is important in screening for elevated IOP. Furthermore, there is a need to comprehend the critical factors that influence IOP in a simple to understand way in the context of clinical values instead of solely relying on correlation coefficients and *p*-values of significance. There are some important clinical implications that may be drawn from this study. Firstly, the regression tree models not only validate the profound influence CCT has on the IOP but also draw attention to the importance of corneal thickness measurements outside the corneal optical zone. The regression tree models further provide eye care clinicians with a realistic approximation of IOP based on the measurements of other anterior segment ocular variables. This information may help practitioners in

detecting which patients require monitoring of IOP on the basis of other routinely measured anterior segment ocular variables.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

N.R. wrote the manuscript and R.H. provided feedback on the structure and content of the manuscript.

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