

Rate of Central Corneal Thickness Changes in Primary Angle Closure Eyes: Long-term Follow-up Results

Hae Min Park

Hanyang University Seoul Hospital

Jiin Choi

Seoul National University Hospital

Won June Lee (✉ wonjunelee@hanyang.ac.kr)

Hanyang University

Ki Bang Uhm

Hanyang University

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Abstract

Background Central corneal thickness (CCT) and its association with intraocular pressure, which is a pivotal parameter in glaucoma management, has previously been reported. In this study, we intended to investigate the long-term change of CCT in terms of rate in eyes with primary angle closure (PAC). Additionally, we aimed to analyze events that could affect CCT.

Methods In this retrospective study, 27 patients with PAC who had a follow-up period of more than five years were evaluated. The rate of CCT changes from baseline was evaluated from the serial CCT measurements over the average follow-up period. The pattern of CCT change rate according to modes of treatment and history of angle closure attack was analyzed using the repeated linear mixed model analysis.

Results A total of 52 eyes were enrolled. The CCT reduction rate of the entire study population was $-0.72 \pm 0.22 \mu\text{m}/\text{yr}$ ($P = 0.001$) with statistical significance. The CCT thinning rate of the laser peripheral iridotomy (PI) group was $-0.53 \pm 0.25 \mu\text{m}/\text{yr}$ ($P = 0.034$), that of the surgical trabeculectomy group was $-1.32 \pm 0.43 \mu\text{m}/\text{yr}$ ($P = 0.002$), and it was not statistically significant ($P = 0.112$). The rate of CCT thinning in patients with a history of acute angle closure attack was $-0.81 \pm 0.31 \mu\text{m}/\text{yr}$ ($P = 0.009$) and that in patients without an attack was $-0.63 \pm 0.30 \mu\text{m}/\text{yr}$ ($P = 0.001$), and it was not statistically significant ($P = 0.680$). Baseline CCT appeared to be the only significant factor affecting the rate of CCT changes ($P < 0.001$).

Conclusions We found a significant reduction in CCT over a long-time observation period in PAC eyes. We also found that the rates of CCT reduction were not affected by different treatment modalities or acute angle closure attack. The analysis of long-term CCT changes in conjunction with baseline CCT would also be helpful in the clinical evaluation of the PAC patients.

Précis

Significant reduction in central corneal thickness (CCT) was observed over a long-time period in primary angle closure eyes. The rates of CCT reduction were not affected by treatment modalities or angle closure attack but affected by baseline CCT.

Background

As far as is known, intraocular pressure (IOP) is the only modifiable risk factor for glaucoma, which is a multivariate figure and small error of any variable can result in under- or over-estimation, which may significantly affect treatment and prognosis.[1, 2]

Primary angle closure (PAC) is a more common form of glaucoma in Asians compared to other ethnicities. It is part of a broader disease spectrum that includes primary angle closure suspect, PACS, primary angle closure glaucoma, PACG, and PAC. PAC is a condition with physical narrowing of the anterior chamber owing to synechial or appositional forces, which then leads to progressive damage of the optic nerve. In the case of acute angle closure, a rapid increase of IOP causes swelling and endothelial damage of cornea, resulting in various biomechanical changes. Furthermore, many recent publications have suggested that long-term use of anti-glaucoma medications, laser procedures, and surgeries affect corneal biomechanics, such as central corneal thickness (CCT).[3, 4]

The importance of CCT in glaucoma is well-established. It is widely accepted that true IOP with thinner cornea is higher than its measurement, and vice versa. Famously, the ocular hypertension treatment study, European glaucoma prevention study, and Barbados eye study showed that CCT could be a risk factor for development and progression of glaucoma disease.[5-8] Currently, multiple studies focus on its relationship to multiple types of glaucoma, age, ethnicity, and so on. Unfortunately, only a few of them showed that CCT is a substantial risk factor for glaucoma, and most of the studies were short-term.

CCT is important in the evaluation of glaucoma. We believe, understanding the corneal changes in PAC eyes according to time is crucial since PAC itself and even its treatments can induce changes in various corneal parameters.

Based on our literature review, no publication has reported a long-term change of CCT rate, in particular. This study aimed to investigate the long-term rate of CCT change in eyes with PAC.

Methods

The Institutional Review Board of Hanyang University Hospital approved this study (IRB No. 2020-04-057-001). The study design followed the tenets of the Declaration of Helsinki for biomedical research.

Subjects

A total of 27 patients with PAC who were followed-up for more than five years at the Department of Ophthalmology of Hanyang University Hospital from January 2002 to December 2010 were enrolled in this study and their medical charts were retrospectively reviewed. Only the patients with PAC were included in the study. Clinical definitions of PAC and its disease spectrums are further described in oncoming section. Exclusion criteria included secondary angle closure due to any possible causes, such as neovascular, uveitic glaucoma or trauma, corneal disorders that prevent accurate measurements, previous history of ocular surgery, trauma and other ocular disorders after intraocular surgery. Patients with less than 5-year follow-up period were also excluded from the study.

All subjects underwent a complete ophthalmologic examination, including visual acuity testing, manifest refraction assessment, slit-lamp examination, IOP measurements using Goldmann applanation

tonometry, gonioscopy, dilated fundus examination, axial length measurement (IOLMaster; Carl Zeiss Meditec, Dublin, Ca, USA, Aviso; Quantel medical, Quebec, Canada), stereo-disc photography and red-free RNFL photography (TRC-50X; Topcon Corporation, Tokyo, Japan, F-10; Nidek, Gamagori, Japan), and Swedish interactive thresholding algorithm (SITA) 30-2 perimetry (Humphrey Field Analyzer II; Carl Zeiss Meditec, Jena, Germany). The CCT measurements were performed using an ultrasound pachymeter (Tomey SP-3000; Tomey Corporation, Nagoya, Japan) by the same technician, recording a mean of ten consecutive readings. Above explained ophthalmologic examinations were performed every year for all study patients.

PAC and its disease spectrum

The latest classification scheme by the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) describes features of the PAC spectrum (PACS, PAC, PACG). Accordingly, PAC was defined as present in an eye with an “occludable angle” with normal IOP, less than 21 mmHg. The occludable angle was defined as when the posterior trabecular meshwork was not visible on the nonindentation gonioscopy for at least two quadrants at the primary position. PAC was defined as PACS eye with features of increased IOP, trabecular obstruction, such as peripheral anterior synechiae (PAS), increased IOP, iris whirling, and glaucomflecken. Both PAC and PACS should not have had glaucomatous optic damage. PACG was defined as the presence of glaucomatous optic neuropathy with compatible visual field loss in an association with occludable angle.[9]

In this study, a single glaucoma specialist (KBU) made clinical diagnoses using non-indentation gonioscopy. All surgical and laser treatment decisions were made and undertaken by a glaucoma specialist (KBU). The laser peripheral iridotomy (PI) was done for patients with acute angle closure by the trained doctor mentioned above. Furthermore, prophylactic PI was performed for patients without an attack, who were considered to have PAC in a broad sense. Trabeculectomy was performed in cases with severe corneal edema or failed PI, such as persistent IOP or progression of glaucomatous damage after PI.

PI was performed in a standard manner. After administration of 2% pilocarpine eye drops, PI was done using argon and Nd:YAG lasers, sequentially. The argon laser was used to irradiate the iris, using an Abraham lens. First, 3-6 pulses at a power of 200 mW and a spot diameter of 200 micron with a duration of 0.2 seconds for iris extension, was performed. Then, 10-40 pulses at 800 mW power, the spot diameter of 50 micron, and a duration of 0.05 to create perforation in the iris were done. Irradiations were applied to the superior iris in order to avoid corneal complications. Finally, pulses of 3.5 to 5.0 mJ of the Nd:YAG laser was used for complete perforation of the wound. Preoperatively, the administration of anti-glaucoma medications and steroid medications were used for one week. When IOP was not adequately controlled, even after surgical or laser procedures, additional anti-glaucoma medications were prescribed by the single glaucoma specialist (KBU).

Calculation of Central Corneal Thickness Changing Rates & Statistical Analyses

All statistical tests were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Patient characteristics with continuous variables were expressed as the mean \pm SD, and nominal variables were expressed as frequencies and percentages. The normality of the distribution of the CCT scores was verified using the Shapiro-Wilk's test. The rate of CCT changes from baseline was determined from the serial measurements using repeated linear mixed model analysis (expressed in μm per year), with a restricted maximum likelihood estimation. Fixed effects were treatment group (trabeculectomy vs. PI and angle closure attack vs. no attack), time of measurement, and the treatment group by time interaction. The rates of change were compared among groups through testing of the interaction term in the linear mixed models. In this model, the treatment by time interaction was not statistically significant. It indicates that there were no differential changes in CCT over time, depending on treatment groups. The covariance pattern between the repeated measurements was assumed to be compound symmetry. We considered different forms of the random effects terms ranging from the simplest model with no random effects to the largest model with random intercepts and random slopes. We computed the Akaike information criterion (AIC) for a set of candidate models with different forms of random effects and selected the one with the smallest AIC value indicating better fitting model. Finally, we applied eye-specific random effects model. Additionally, we analyzed the associated CCT change rate in PAC patients with clinicopathological factors of interest using a linear mixed model, and estimate, SE, and its P-values were calculated. The level of significance was set at P-value < 0.05 .

Results

The study evaluated 54 eyes of 27 patients with PAC, and two eyes of one patient, which developed bullous keratopathy due to failure of IOP control, were excluded. Finally, 52 eyes of 26 patients were analyzed.

Clinical Demographics

Table 1 shows the clinical demographics of all patients at the time of enrollment. A total of 40 eyes underwent PI only. A total of 12 patients had trabeculectomy. The latter group included patients who underwent a PI before trabeculectomy. Twenty-three eyes had a history of angle closure attack.

The average number of the examinations was 7.0 ± 2.1 (range, 4–10) over a mean follow up period of 94.5 ± 28.7 months (range, 66–134 months). Most of the study population consisted of females (92.3% of all patients) with a mean age of 63.4 ± 8.7 years (range, 48 –78 years). The baseline CCT was $549.1 \pm 29.2 \mu\text{m}$ (range, 484–619 μm), and mean presenting IOP was 29.6 ± 18.2 mmHg (range, 6–64 mmHg).

Central corneal thickness change rate

In each group there was a statistically significant reduction in CCT, as indicated in Supplementary Table 1. The CCT thinning rate of all enrolled patients was $-0.72 \pm 0.22 \mu\text{m}/\text{yr}$, and it was a statistically significant reduction ($P = 0.001$).

Overall, the CCT thinning rate in each of the two groups was statistically significant. The CCT thinning rate of the PI group was $-0.53 \pm 0.25 \mu\text{m}/\text{yr}$, that of the trabeculectomy group was $-1.32 \pm 0.43 \mu\text{m}/\text{yr}$ ($P = 0.034$ and $P = 0.002$, respectively). However, the statistical analysis showed that a higher CCT thinning rate of the trabeculectomy group was not statistically significant ($P = 0.112$) (Table 2 and Figure 1). Similar results were observed in CCT comparison with regard to the presence of angle closure attack. The rate of CCT thinning in patients with a history of acute angle closure attack was $-0.81 \pm 0.31 \mu\text{m}/\text{yr}$ and that in patients without an attack was $-0.63 \pm 0.30 \mu\text{m}/\text{yr}$ ($P = 0.009$ and $P = 0.001$, respectively). There was no statistically significant difference in the CCT thinning rate between the two groups ($P = 0.680$). (Table 2 and Figure 2)

Figures 1 and 2 show CCT changes during the follow-up period, with the maximum being close to 11 years. It demonstrates the changes of CCT over time in all study patients, and that divided by subgroups (trabeculectomy vs. PI, and angle closure attack vs. no attack). The mean CCT changes were schematically drawn to compare the total study groups and the subgroups easily.

The results of the analysis for identifying factors associated with the CCT change rates are summarized in Table 3. Only baseline CCT was associated with the rates of its thinning ($P < 0.0001$). In other words, higher baseline value was associated with a higher rate of CCT reduction. However, in this statistical analysis, CCT change rate was not significantly associated with age ($P = 0.297$), sex ($P = 0.231$), IOP ($P = 0.295$), type of intervention ($P = 0.913$), and presence of angle closure attack ($P = 0.238$).

Discussion

Biometrics of PAC eyes have been subjected to study for many years. Recent interest in CCT is due to its influence on the accuracy of IOP measurements.[10] In this retrospective study, we found a marked reduction of CCT in all PAC patients enrolled in this study. However, no significant difference was observed regardless of acute angle closure attack and modes of glaucoma treatment. Only a few studies observed long-term reduction of CCT, especially in the study population with PAC. We believe this study has its originality in that it conducted a long-term evaluation of CCT changes in PAC patients and analyzed it with the concept of rate.

Several studies, mostly cross-sectional, have compared CCT in normal controls and other glaucoma subtypes, including PAC. The results of the studies mostly suggested that there was no statistically significant difference in CCT among glaucoma subtypes and normal controls.[11-13] A large population study in Beijing conducted by Xu et al. also suggested no significant difference between glaucomatous and normal eyes.[14]

Comparable to our study designs, some studies have studied CCT changes in PAC eyes only. Chen et al. studied corneal status in the PAC disease spectrum. In this study, PAC eyes with a history of ACG attack were compared with fellow PAC eyes without attack and found no significant difference in CCT between the two groups.[15] Although previous studies published significant results with large study groups, the weakness was that they were conducted in the short-term. We believe long-term change of corneal characteristics would be more applicable in assessing glaucoma since corneal characteristics are changeable with aging and corneal insults, such as surgeries, angle closure attack, and topical medications.

In this study, final mean CCT and its change rate were not significantly different between the PI and trabeculectomy groups. The same result was observed for eyes with and without acute angle closure attack. This is consistent with a few previous studies, Pillunat et al. investigated corneal biomechanical changes after trabeculectomy, and showed that despite a decline in IOP, CCT was not altered.[16] A few other studies suggested similar findings with PI.[17, 18]

Instead of CCT, multiple studies have shown irreversible corneal endothelial damage caused by surgeries, laser procedures, and even topical medications.[16-22] In relevance to the field of glaucoma, many researchers have studied associations between the corneal endothelial loss with glaucoma subtypes. Shiota et al. investigated corneal endothelial status across subtypes of angle closure glaucoma. They found that the previous acute angle closure and chronic PACG had significantly lower endothelial cell density (ECD).[23] At the same time, there are conflicting studies. Varadaraj et al. and Verma et al. studied endothelial changes in the PAC disease spectrum, including eyes with a history of acute angle closure attack and found no significant difference in all groups.[24, 25] Interestingly, a recent study of a rat model showed eyes with acute angle closure had lower ECD at first, but showed a gradual resolution once IOP stabilized to normal levels.[26] It may be more useful to assess endothelial changes since CCT does not reflect the overall corneal status. Unfortunately, we were not able to perform endothelial studies on our study population owing to the retrospective nature of this study. A long-term evaluation of CCT in conjunction with ECD changes is required for future studies, and assessment of corneal status with various parameters will enrich future study results.

The repeated mixed model in this study showed that baseline CCT was the only factor associated with the rate of its reduction. Two possible mechanisms can explain such a finding. First, eyes with thick cornea can be intrinsically prone to CCT thinning. This mechanism requires further study or statistical analysis that directly compares the CCT thinning rate between eyes with a thin cornea and thick cornea. Second, corneal edema caused by an acute angle closure attack or anti-glaucoma procedures can be another possible explanation. Corneal edema can quickly resolve as IOP normalizes, which in turn, can overestimate CCT thinning rate. Correlation with the interval between the acute insult and CCT measurement will be helpful to clarify this finding further.

The primary strength of this study is that the longitudinal change of CCT in the extended time was evaluated, with the maximum follow-up duration being close to 11 years. Another strength is that we

evaluated CCT with account for events that can affect the corneal status, such as acute angle closure attack and surgeries. We are aware of the numerous publications with notable results that studied CCT changes in normal and different glaucoma types.[20-22] However, these studies had a small sample size and, more importantly, had short observation periods, ranging from months to 4–5 years. The cornea is a structure that is prone to change over time. It can change with aging, long-term topical medication use, surgeries, and even diurnally.[27-30] Considering this, we believe that a long-term investigation of CCT concerning acute events is more applicable in glaucoma evaluation than cross-sectional studies of CCT.

Despite the distinct merits of this study entails, there are some limitations. One is that the study has no data regarding CCT changes with age, and that in the normal controls or in other forms of glaucoma. Many published reports are showing a decremending trend of CCT with age, but some show contradictory results. Pang et al. and Day et al. studied CCT and its relationship with glaucoma in Asian and East Asian patients; their results showed statistically significant CCT reduction with increasing age. In this study, the CCT change rate and age were found to have no association. However, since the study only included PAC eyes, comparison with normal controls or other forms of glaucoma is required for a more fair comparison. Another limitation is that other possible confounding factors were not considered in this study. It has been previously reported that systemic diseases, such as diabetes and some anti-glaucoma medications, can affect corneal biometrics. Particularly, prostaglandin analogues, such as latanoprost and travoprost,[20-22, 31] were associated with thinning of CCT in both short-and long-term studies. However, owing to the extensive study period, information on the duration of usage, changes in regimen was difficult to follow-up, as well as to statistically analyze. For this reason, these possible contributing factors were ignored in this study and further study will be required to assess its conduciveness.[32] Additionally, a larger sample size will be required for further studies. This may have been due to the fact that the study was restrospectively designed and included patients with very long-term follow up period, which makes it difficult to collect sufficient sample size. Lastly, as aforementioned, other corneal parameters, such as ECD, were not taken into consideration owing to retrospective nature of this study. Evaluation of PAC eyes with various parameters would be more interesting for future study and more valuable in understanding the true changes in corneal biomechanics of PAC eyes.

Conclusions

To conclude, we found a significant decline in CCT over a long time-period in PAC eyes. The rates of this reduction were not influenced by treatment modalities or the presence of an ACG attack. Instead, baseline CCT appeared to be the only significant factor affecting the rate of its changes. It holds for more future investigations. The analysis of other corneal parameters, such as ECD, in conjunction with CCT would be more interesting and beneficial to understand true corneal biomechanical changes in PAC eyes. Observation of long-term CCT changes by its baseline would also further validate this study's results.

Abbreviations

CCT = central corneal thickness, PAC = primary angle closure, PI = laser peripheral iridotomy, IOP = intraocular pressure, PACS = primary angle closure suspect, PACG = primary angle closure glaucoma, ISGEO = International Society of Geographical and Epidemiological Ophthalmology

Declarations

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Conflicts of Interest: No conflicting relationship exists for any author.

Ethics approval and consent to participate

This non-interventional retrospective chart-review study was approved by the Institutional Review Board of the Hanyang University Hospital (IRB No. 2020-04-057-001), and the committee (Institutional Review Board of the Hanyang University Hospital) waived the need for informed consent from the patients because the data were anonymized.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

No conflicting relationship exists for any author.

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Authors' contributions

Conceptualization: Hae Min Park, Jiin Choi, Won June Lee, Ki Bang Uhm

Data curation: Hae Min Park, Jiin Choi, Won June Lee, Ki Bang Uhm

Formal analysis: Hae Min Park, Jiin Choi, Won June Lee, Ki Bang Uhm

Funding acquisition: Won June Lee

Investigation: Hae Min Park, Jiin Choi, Won June Lee, Ki Bang Uhm

Methodology: Jiin Choi and Won June Lee

Supervision: Won June Lee

Validation: Hae Min Park and Won June Lee

Visualization: Hae Min Park, Jiin Choi, Won June Lee

Writing – original draft: Hae Min Park, Jiin Choi, Won June Lee, Ki Bang Uhm

Writing – review & editing: Hae Min Park, Jiin Choi, Won June Lee, Ki Bang Uhm

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WJL had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors alone are responsible for the content and writing of the paper.

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Authors' information

Not applicable

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Tables

Table 1. Participant demographics

	N = 26, 52 eyes
Age	63.4 ± 8.7
Sex (M:F)	2:24 (7.7%:92.3%)
Initial IOP	29.6 ± 18.2
MD	-6.47 ± 7.24
Axial length	22.55 ± 0.73
Baseline CCT	549.1 ± 29.2
Iridectomy only / Trabeculectomy	40/12 (76.9%/23.1%)
Angle closure attack / no attack	23/29 (44.2%/55.8%)
Follow up duration (months)	94.5 ± 28.7
Examination number	7.0 ± 2.1

IOP indicates intraocular pressure; MD, mean deviation from automated visual field exam; CCT, central corneal thickness.

Table 2. Central corneal thickness change rate according the type of operation and to the presence of acute angle closure attack

	According to the type of operation			
	Total	PI only	Trabeculectomy	P-value*
CCT thinning rate	-0.72 ± 0.22 (P = 0.001)	-0.53 ± 0.25 (P = 0.034)	-1.32 ± 0.43 (P = 0.002)	0.112
	According to the presence of angle closure attack			
	Total	Attack (+)	Attack (-)	P-value**
CCT thinning rate	-0.72 ± 0.22 (P = 0.001)	-0.81 ± 0.31 (P = 0.009)	-0.63 ± 0.30 (P = 0.001)	0.680

CCT indicates central corneal thickness; PI, laser peripheral iridotomy.

* Repeated Measures Linear Mixed Model: Duration as continuous variable & Operation

**Repeated Measures Linear Mixed Model: Duration as continuous variable & angle closure attack

Table 3. Factors associated with central corneal thickness change rate in primary angle closure patients

	Estimate	SE	CI	P-value*
Age	-0.27	0.25	(-0.77, 0.24)	0.297
Sex : Female (vs. Male)	-11.21	9.23	(-29.81, 7.40)	0.231
IOP	-0.27	0.26	(-0.77, 0.24)	0.295
MD	-0.08	0.26	(-0.59, 0.43)	0.768
Axial length	5.25	2.99	(-0.77, 11.28)	0.086
Angle closure attack (vs. No attack)	-5.32	4.45	(-14.28, 3.64)	0.238
Type of intervention	-0.59	5.38	(-11.40, 10.22)	0.913
: Trabeculectomy (reference: PI)				
Baseline CCT	0.81	0.07	(0.67, 0.94)	<0.001
Duration	-0.45	0.34	(-1.13, 0.23)	0.195

IOP indicates intraocular pressure; MD, mean deviation from automated visual field exam; PI, laser peripheral iridotomy; CCT, central corneal thickness.

*Repeated Measures Linear Mixed Model

Figures

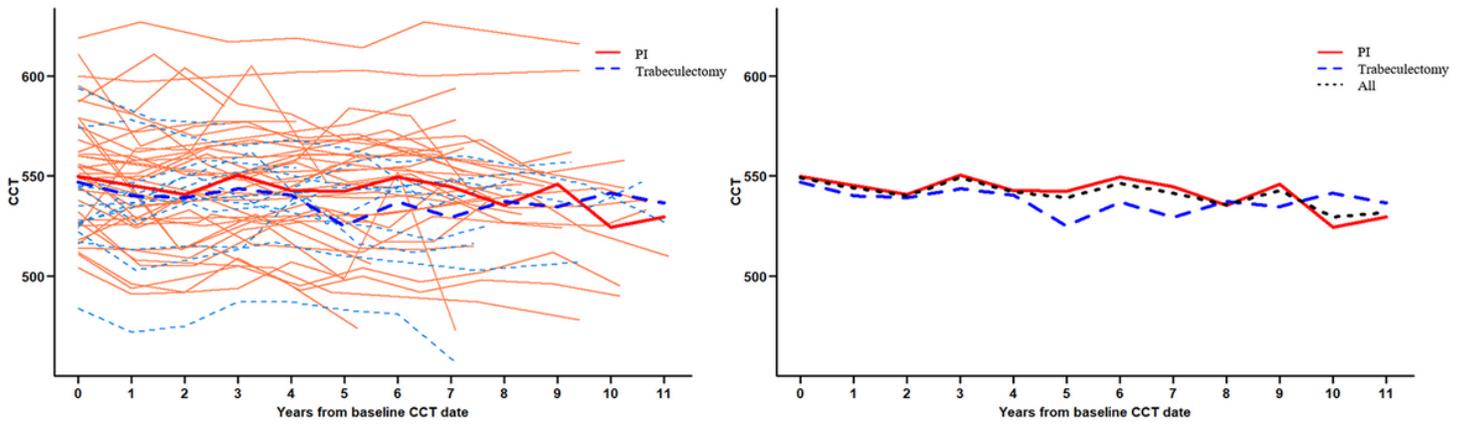


Figure 1

Comparison of central corneal thickness changes between the trabeculectomy and laser peripheral iridectomy only groups over time Changes of central corneal thickness (CCT) over 11-year period. The CCT of the trabeculectomy group is lower than that of the laser peripheral iridectomy (PI) only group, which revealed to be statistically insignificant ($P = 0.112$). Note: bold lines represent the mean value.

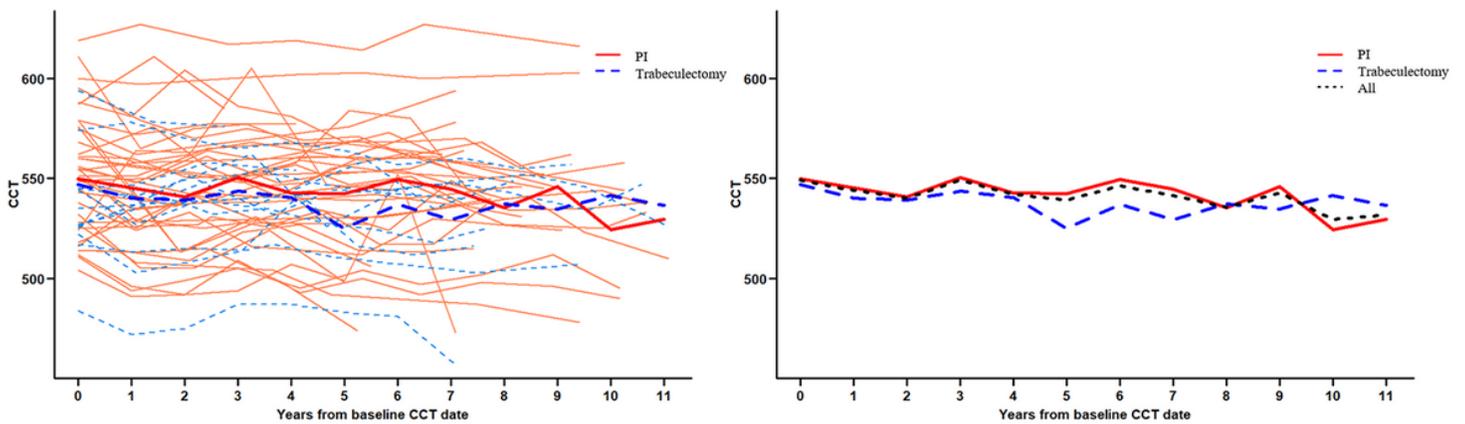


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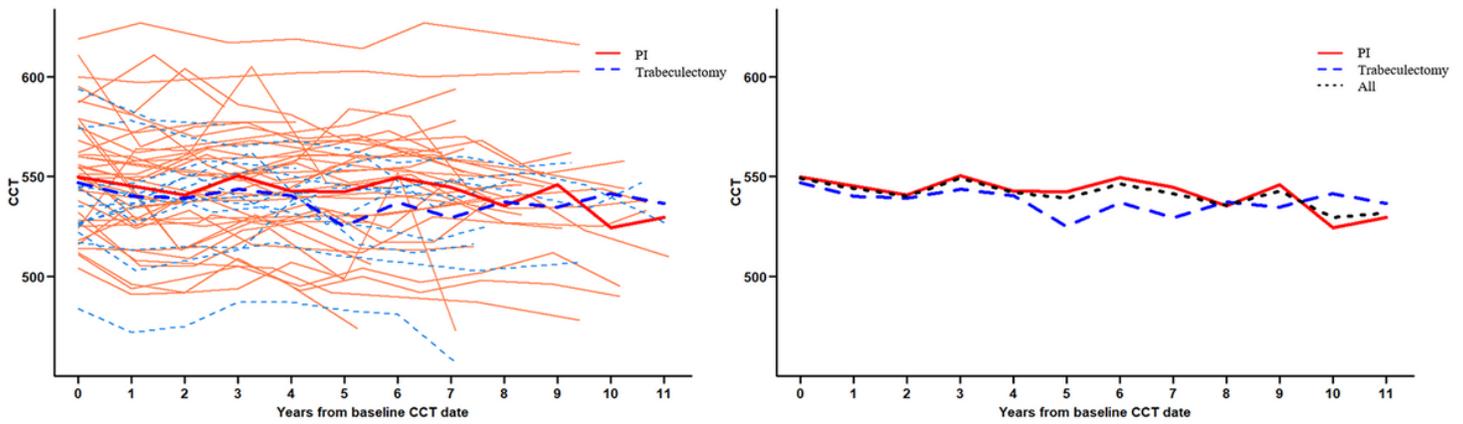


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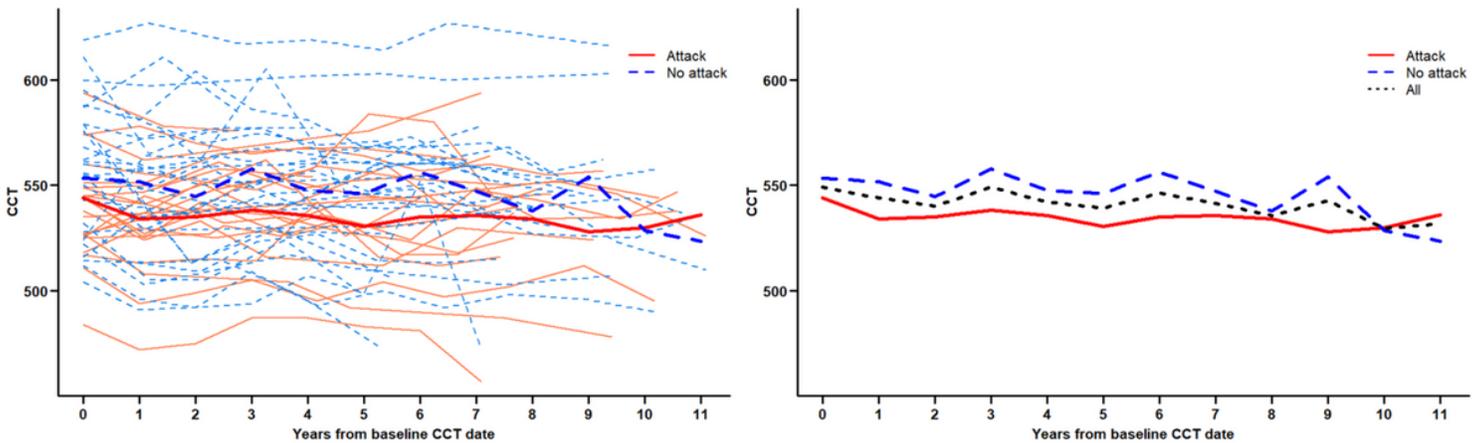


Figure 2

Comparison of central corneal thickness changes between the two groups: with angle closure attack and without an attack. Changes of central corneal thickness (CCT) over 11-year period. The CCT of the study group with an acute angle closure attack seems to be lower than that of the study group without an attack. Statistical analysis showed there was no statistical significance between the central corneal thickness thinning rate of the two groups ($P = 0.680$). Note: bold lines represent the mean value.

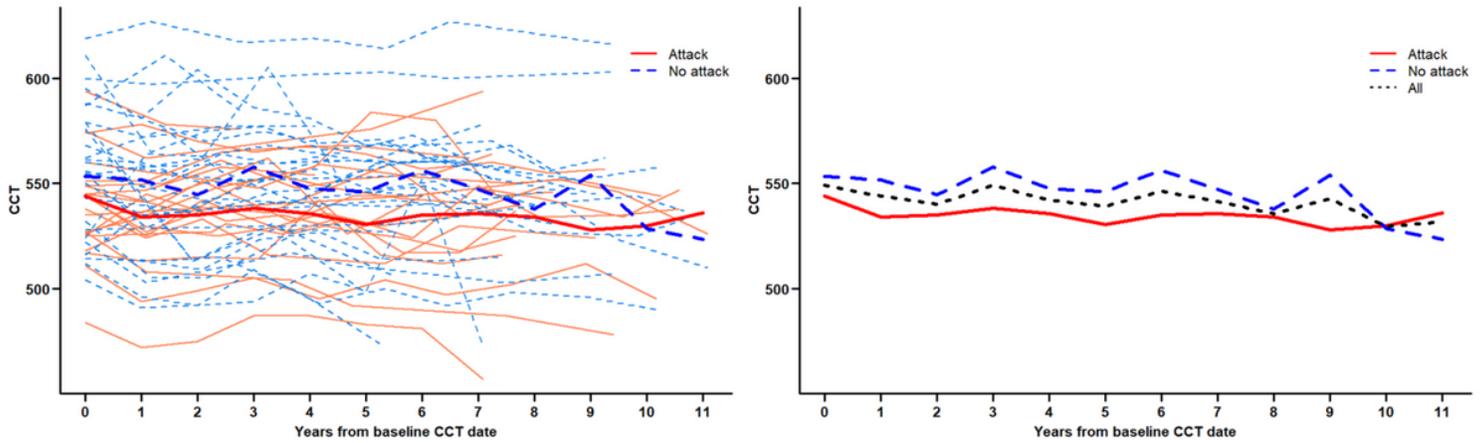


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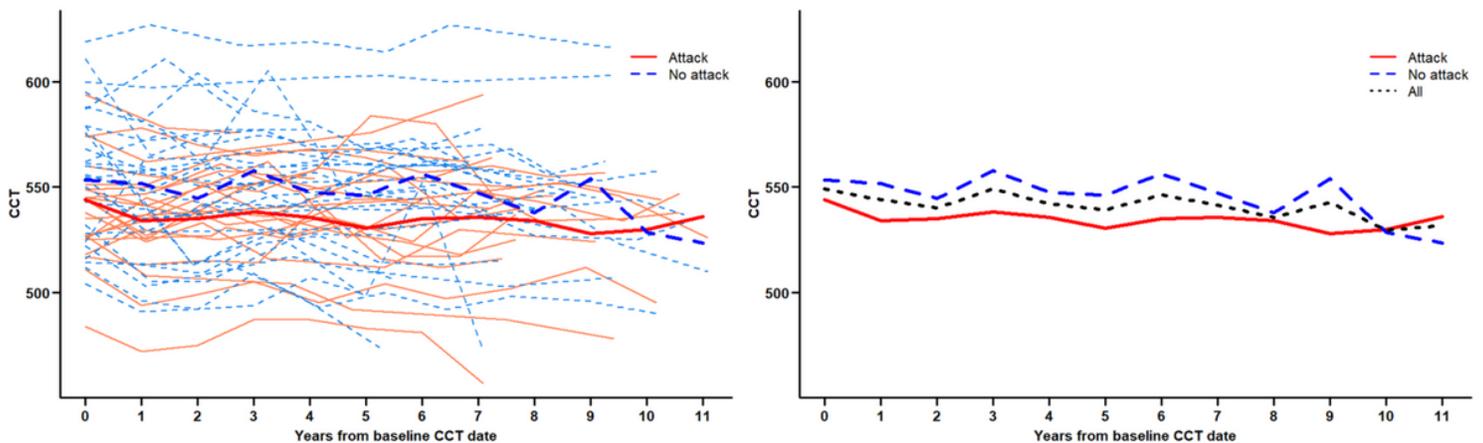


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Supplementary Files

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- [Supplementarytable1.pdf](#)
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