Factors leading to high intraocular pressure in intraocular device-associated uveitis (IDAU): a nested case control study

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Clinical Sciences
FACULTY OF MEDICINE
Chulalongkorn University
Academic Year 2022

ปัจจัยที่ทำให้เกิดความดันลูกตาสูงในคนไข้ม่านตาอักเสบที่เกิดจากอุปกรณ์ปลูกถ่ายภายในลูกตา: การศึกษาแบบมีกลุ่มเปรียบเทียบ

นายจักรกฤษณ์ จูห้อง

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาเวชศาสตร์คลินิก ไม่สังกัดภาควิชา/เทียบเท่า
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2565

Thesis Title	Factors leading to high intraocular pressure in intraocular device-associated uveitis (IDAU): a nested case control study
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Field of Study	Clinical Sciences
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จักรกฤษณ์ จูห้อง : ปัจจัยที่ทำให้เกิดความดันลูกตาสูงในคนไข้ม่านตาอักเสบที่เกิดจากอุปกรณ์ปลูกถ่ายภายในลูกตา: การศึกษาแบบมีกลุ่มเปรียบเทียบ. (Factors leading to high intraocular pressure in intraocular device-associated uveitis (IDAU): a nested case control study) อ.ที่ปรึกษาหลัก : รศ. นพ.กฤษณ์ พงศ์พิรุฬห์

วัตถุประสงค์: เพื่อศึกษาปัจจัยเสี่ยงที่นำไปสู่ความดันลูกตาสูง (IOP) ในผู้ป่วยที่มีภาวะช่องหน้าม่านตาอักเสบสัมพันธ์กับอุปกรณ์ปลูกถ่ายภายในลูกตา และเพื่ออธิบายลักษณะทางคลินิกของภาวะ ม่านตาอักเสบ-ต้อหิน-เลือดออกในช่องหน้าลูกตา วิธีการวิจัย: การศึกษานี้เป็นแบบ Retrospective nested case-control ในโครงการศึกษาระยะยาวแบบไปข้างหน้าของคลินิกจักษุภูมิคุ้มกันและการอักเสบ ของโรงพยาบาลจุฬาลงกรณ์ กรุงเทพฯ ประเทศไทย ระหว่างปี 2557-2565 (CU2C) โดยในการศึกษานี้ มีจำนวนผู้เข้าร่วมวิจัยทั้งหมด 375 คน ในจำนวนนี้มี 30 คนที่วินิจฉัยว่ามีภาวะม่านตาอักเสบที่เกิดจากอุปกรณ์ปลูกถ่ายภายในลูกตา ร่วมกับมีความดันลูกตาสูง ซึ่งจัดอยู่ในกลุ่มที่เป็นโรค (cases) และอาสาสมัครจำนวน 60 คนที่มีภาวะม่านตาอักเสบที่เกิดจากอุปกรณ์ปลูกถ่ายภายในลูกตา ร่วมกับมีความดันตาปกติ ซึ่งถูกจัดเป็นกลุ่มควบคุม (controls) และนำข้อมูลมาวิเคราะห์ทีละปัจจัยโดยใช้เทคนิค Univariate analysis และวิเคราะห์ทีละหลายปัจจัยโดยใช้เทคนิค Multivariate binary logistic regression analysis ปัจจัยที่นำวิเคราะห์ประกอบด้วย อายุ เพศ โรคประจำตัว ภาวะลูกตายาว ภาวะสายตาสั้น ภาวะลูกตาหลังผ่าตัดน้ำวุ้นตา เยื่อหุ้มหลังเลนส์แก้วตาฉีกขาด ภาวะม่านตาบางจากการเสียดสีกับชิ้นส่วนของเลนส์ เลนส์แก้วตาเทียมอยู่ผิดตำแหน่ง และการใส่เลนส์แก้วตาเทียมชนิดชิ้นเดียวในช่องหลังม่านตา ผลการวิจัย: ปัจจัยที่เกี่ยวข้องกับความดันลูกตาสูง (IOP) ในผู้ป่วยที่มีภาวะช่องหน้าม่านตาอักเสบสัมพันธ์กับอุปกรณ์ปลูกถ่ายภายในลูกตาอย่างมีนัยสำคัญทางสถิติ ได้แก่ เลนส์แก้วตาเทียมอยู่ผิดตำแหน่ง (adjusted odds ratio [AOR]: 8.30, 95% CI 1.25-54.76), ภาวะลูกตายาว (AOR: 8.08, 95% CI 1.18- 20.20) และอายุ (AOR: 1.18, 95% CI 1.07-1.31)

สาขาวิชา	เวชศาสตร์คลินิก	ลายมือชื่อนิสิต .....
ปีการศึกษา	2565	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

6478001530 : MAJOR CLINICAL SCIENCES

KEYWORD: uveitis-glaucoma-hyphema syndrome, UGH, Ellingson syndrome, malposition intraocular device, pigment dispersion, vitreous hemorrhage, cataract surgery

Jakkrit Juhong : Factors leading to high intraocular pressure in intraocular device-associated uveitis (IDAU): a nested case control study. Advisor: Assoc. Prof. Dr. KRIT PONGPIRUL, Ph.D.

Purpose: To describe the clinical pattern of uveitis–glaucoma–hyphaema (UGH) syndrome and to evaluate the risk factors leading to high intraocular pressure among intraocular device-associated uveitis (IDAU) patients using the Chulalongkorn University Uveitis Cohort (CU^2C) database.

Methods: A retrospective nested case control study was conducted in a cohort of 375 subjects who were followed up in a uveitis clinic at King Chulalongkorn Memorial Hospital (KCMH), Bangkok, Thailand, from 2014 to 2022. Thirty subjects with IDAU with increased intraocular pressure (IOP) were included in the case group, and 60 subjects with IDAU without increased intraocular pressure were selected from the CU^2C database as controls. By using univariate analysis and multivariate binary logistic regression analysis, the odds ratio (OR) and its 95% confidence interval (95% CI) were calculated between increasing IOP in IDAU subjects and other potential associated factors, including age, sex, comorbidities, long eye, myopia, vitrectomized eyes, ruptured posterior capsule, transillumination iris defect (TID) , pseudophacodonesis, malpositioned IOL, and single-piece IOL in sulcus.

Results: We retrospectively identified 90 patients who developed IDAU. Following a one-to-two case–control ratio, 30 case patients and 60 control patients were included. Three factors were significantly associated with high intraocular pressure in IDAU. These included intraocular lens (IOL) malposition (AOR: 8.30, 95% CI 1.25 to 54.76), long eye (AOR: 8.08, 95% CI 1.18 to 20.20) and age (AOR: 1.18, 95% CI 1.07 to 1.31). There was no statistical evidence of effects of hypertension, ruptured posterior capsule, vitrectomized eye, TID, pseudophacodonesis and single-piece IOL in sulcus on high IOP in IDAU.

Conclusion: We demonstrated significant associations between various factors and high intraocular pressure in IDAU. Our findings provide useful information about potential risk factors to help physicians prevent and be aware of the progression of increasing IOP in IDAU.

Field of Study:	Clinical Sciences	Student's Signature .....
Academic Year:	2022	Advisor's Signature .....

ACKNOWLEDGEMENTS

I humbly extend my heartfelt appreciation to my esteemed advisor Dr. Thanapong Somkijrungrot and the distinguished Assoc. Prof. Krit Pongpirul, PhD for their invaluable guidance, unwavering support, and boundless patience throughout the arduous journey of my thesis project. Their exceptional expertise and experience in the field of statistics have been a constant source of inspiration and direction.

I am immensely grateful to my esteemed defense committee, Prof. Dr. Wiroj Jiamjarasrangsi, Ph.D., and Prof. Dr. Kessara Pathanapitoon, Ph.D., for their benevolent provision of constructive feedback, and their vast reservoirs of knowledge and expertise. Their valuable insights have been instrumental in shaping the outcome of this study.

I would also like to express my sincere gratitude to the erudite Dr. Somtaporn Ueathaweephol for her invaluable assistance in the collection of research data, and for her expert advice that proved to be of immense value.

I extend my deep appreciation to the entire staff at Chula Retina Unit for their support and for their gracious granting of access to their facilities for this study.

Finally, I would like to express my sincerest gratitude to my family for their understanding, encouragement, boundless love, and selfless sacrifices in nurturing and equipping me for my future. Their unswerving confidence in my capabilities has kept me motivated and resolute throughout my thesis journey.

Jakkrit Juhong

TABLE OF CONTENTS

List of Tables

List of Figures

Chapter 1 Introduction

Background and rationale

Uveitis–glaucoma–hyphema syndrome (UGH syndrome, or "Ellingson" Syndrome) is a rare condition caused by malpositioned or subluxed intraocular lens (IOL), which results in mechanical chaffing to uveal tissue (iris, ciliary body, iridocorneal angle) leading to a wide spectrum of clinical pictures ranging from mild iris transillumination defect to pigment dispersion, anterior segment inflammation, microscopic hyphema, hyphema, elevated intraocular pressure, cystoid macular edema and vitreous hemorrhage[1]. UGH syndrome usually develop months to years following cataract surgery, however it can also develop immediately after the procedure[2]. This syndrome can develop after the implantation of any anterior segment device[3-5], yet it is most commonly associated to anterior chamber lens implants[2, 3, 6]. Because of the wide range of non-specific clinical signs and symptoms associated with UGH, diagnosis is not always straightforward.

The pathogenesis and risk factors for UGH syndrome remain controversial, thus limiting their causal inference. Furthermore, a well-designed study including all of the abovementioned issues has yet to be conducted. Furthermore, development of secondary glaucoma causes a potentially sight-threatening condition that can end in blindness; thus, misdiagnoses of UGH syndrome can lead to unnecessary testing and serious sight-threatening conditions[3-5].

We consider that the term "UGH syndrome" is nonspecific and does not correspond to the major pathogenesis of the syndrome, which is caused by intraocular implantation, particularly of IOLs. As a result, throughout this study, we prefer to use the term "intraocular device associated uveitis; IDAU" instead of "UGH syndrome". The aims of this study were to investigate the clinical pattern of IDAU in terms of the consequences of clinical findings (uveitis, glaucoma, and hyphema) and to evaluate the risk factors leading to high IOP among IDAU patients by conducting a population-

based retrospective nested case-control study using the Chulalongkorn University Uveitis Cohort (CU^{2}C) database[7], which is an ongoing cohort study that began in August 2014 in King Chulalongkorn Memorial Hospital (KCMH), Thailand. This study provides a better understanding of UGH pathogenesis, natural courses, and the factors that cause high intraocular pressure in IDAU patients. In addition, to our knowledge, we are the first study to evaluate UGH syndrome using a nested case-control design.

Hypothesis

- The potential factors such as age, sex, comorbidities, high axial length, myopia, vitrectomized eyes, ruptured posterior capsule, transillumination iris defect (TID), malpositioned IOL, and single-piece IOL in the sulcus are associated with to high intraocular pressure in IDAU
- The first clinical finding of UGH is anterior uveitis follow by increased intraocular pressure and intraocular bleeding.

Objectives

- To investigate the risk factors for high intraocular pressure in IDAU
- To investigate the clinical pattern of IDAU

Chapter 2 Literature Review

In 1978, Ellingson was the first to describe Uveitis-Glaucoma-Hyphaema syndrome (UGH syndrome), also known as "Ellingson syndrome," which occurs due to iris chafing and erosions associated with first-generation rigid anterior chamber (AC) intraocular lenses (IOLs). This syndrome leads to uveitis, intraocular hemorrhage, and/or glaucoma[6]. Following this discovery, UGH syndrome was recognized as an exceptionally rare condition resulting from malposition or dislocation of intraocular lenses, causing mechanical chafing of uveal tissues such as the iris, ciliary body, and iridocorneal angle. This condition presents with a wide range of clinical manifestations, including mild transitory intraocular inflammation, pigment dispersion, microscopic hyphema, hyphema, elevated intraocular pressure (IOP), cystoid macular edema (CME), and vitreous hemorrhage[6, 8].

Although UGH syndrome is extremely rare when an intraocular lens is placed in the capsular bag with an intact posterior capsule, various types of lens material and positioning can still lead to UGH syndrome, even in the presence of an in-the-bag IOL. This occurrence is often attributed to inappropriate sizing or positioning of the IOL[9-11]. The existing literature on intraocular device-related UGH syndrome is summarized in Table 1.

Table 1 Reviewed studies of intraocular device-related UGH

Study	Number of cases	Mechanism of UGH	Treatment	Note
Mark VIII AC IOLs				
Ellingson (1978)[6]	7	Mechanical chafing between rigid AC IOLs and iris/iridocorneal angle	IOL explantation and exchange	This study first described UGH syndrome.

PMMA AC IOLs				
Robert et al. (1993)[12]	2	Mechanical chafing between angle supported rigid AC IOLs and iris/iridocorneal angle	IOL explantation and exchange	-
Marques et al. (2007)[13]	5 (4 AC-IOLs, 1 PC-IOLs)			
Iris-fixated IOLs				
Mamalis et al. (1991)[14]	2	Mechanical chafing between iris-fixated IOLs and iris	IOL explantation and exchange	
Robert et al. (1993)[12]	5			
Single piece IOLs in Sulcus				
Davies et al. (2016)[15]	9	Mechanical chafing between IOLs and iris	IOL explantation and exchange	
Chan et al. (2015)[16]	9	Mechanical chafing between IOLs and iris	IOL explantation and exchange	
3 Piece-IOLs in Sulcus				
Walland (2017)[17]	1	Mechanical chafing between iris and PMMA IOL haptic in sulcus	Laser iridoplasty on the iris-haptic contact site	This study highlights the importance of managing each UGH case according to its specific mechanism of uveal-IOL contact, without IOL explantation or exchange.
Singh et al.	6	Reverse pupillary	Laser peripheral iridotomy	

(2015)[18]		block in sulcus-placed PC IOLs in patient with **axial myopia, and postvitrectomized eyes**		
Wardnani et al. (2019)[19]	1	Displacement of a single haptic in the sulcus	Amputation of this haptic	
Scleral-sutured lenses				
Du et al. (2020)[20]	1	Mechanical chafing between IOL haptic and iris due to malpositioned IOL haptics pushing the root of the iris forward.	IOL explantation	This study demonstrates that repeated surgery and implantation/explantation causing uveal tissue trauma is a risk factor for the UGH syndrome.
Single-piece acrylic IOLs in the capsular bag				
Zhang et al. (2014)[21]	2	Mechanical chafing between single-piece acrylic IOLs in the capsular bag and the iris due to zonular laxity	Capsular tension ring to stabilize the IOL-iris complex Retracted a chaffed ciliary process by endocyclophotocoagulation in a patient with extensive capsular fibrosis	This study highlights that multipiece acrylic IOL with round polypropylene (Prolene) haptics may be a protective effect due to its rounded polypropylene haptics do not have sharp edges preventing mechanical chafing and help to stabilize the capsular bag and zonule.
Jasinskas et al. (2018)[22]	3	Mechanical chafing between single-piece acrylic IOLs	IOL sutured to the iris to stabilize the IOL-iris complex	

		in the capsular bag and the iris due to zonular laxity		
UGH syndrome caused by other intraocular implants				
Stella et al. (2009)[4]	1	Mechanical chafing between a cosmetic iris implant and iris	Combined trabeculectomy and removal of the iris implants	
Cheung et al. (2018)[5]	1	Iris trauma from the anteriorly displaced Cionni ring fixation eyelet	Repositioning of the ring and fixing to the sclera	
Hou et al. (2019)[3]	1	Posteriorly placed EX-PRESS shunt implant	Localized laser iridoplasty around the shunt	

However, due to advancements in treatment technology, improvements in lens materials and designs, and the increasing trend of posterior chamber IOL (PCIOL) implantation, the incidence of UGH syndrome has declined over the years from 2.2 to 3% to 0.4 to 1.2% over one year [23, 24]. Despite this decline, the prevalence of UGH caused by ocular devices other than IOLs is increasing, particularly with the rise in intraocular device implantation for glaucoma surgical treatments. For example, a case report by Andrew Hou et al. in 2019 describes UGH syndrome in a patient who underwent an EX-PRESS shunt implantation, highlighting the potential for UGH syndrome to occur with various types of intraocular devices[3].

Notably, UGH syndrome can still occur even with a properly placed IOL in the capsular bag. A rare manifestation of UGH syndrome was reported by Swathi Vallabh Badakere et al. in 2016, where a patient underwent uneventful cataract surgery with a posterior chamber IOL positioned within the bag, covered by a capsulorrhexis margin. However, the use of dilated gonioscopy revealed superior

haptic displacement due to a tear in the equatorial bag, leading to hyphema, anterior chamber inflammation, and high intraocular pressure[9].

The clinical manifestations of UGH syndrome have evolved significantly from the classic descriptions. Notably, the type of IOL used is a major difference in current UGH presentations. Modern anterior chamber implants have been developed with improved design and materials, resulting in fewer complications compared to their previous versions. Additionally, there has been a declining trend in the use of anterior chamber IOLs. Surgeons now prefer posterior chamber IOLs inserted in the ciliary sulcus, scleral-fixed (by suture or externalized haptics), or iris-sutured for cases with insufficient capsular support during complicated cataract surgeries. However, the clinical evidence supporting the superiority of any posterior chamber fixation method over a properly positioned anterior chamber IOL remains insufficient [25, 26].

Currently, UGH syndrome is most commonly associated with posterior chamber IOLs placed in the sulcus or fixed to the sclera or iris, rather than being implanted within the capsular bag [25]. The use of single-piece acrylic lenses in the sulcus is another factor contributing to UGH syndrome, despite the high incidence of complications such as hemorrhage, increased intraocular pressure, and iris transillumination defects. Complications may arise when one haptic of a single-piece acrylic lens is positioned outside the capsular bag due to the absence of optic-haptic vault, haptic edge design, and haptic material compatibility with uveal tissue [25].

The pathogenesis of UGH syndrome is complex and non-specific, involving various common factors. Uveal chafing from an intraocular implant can cause pigment dispersion, uveitis, and eventually, iris neovascularization. Malpositioned anterior chamber IOL haptics, anterior synechiae, pigment dispersion, or the presence of red blood or inflammatory cells can all damage or obstruct the trabecular meshwork, resulting in increased intraocular pressure. Hyphema formation can occur due to iris vascular damage [1]. In a comprehensive series involving 71 patients with UGH syndrome, it was observed that pseudophacodonesis served as a risk factor for the

development of UGH syndrome. Furthermore, their analysis indicated that the use of blood thinners did not contribute to an increased risk of UGH syndrome[2].

Diagnosing UGH syndrome does not require the complete triad of features to be present; the presence of a single feature along with its accompanying anatomical abnormality is sufficient [25]. Clinical examinations often overlook findings relevant to UGH syndrome. The clinical course of UGH can vary and is nonspecific, with episodes of blurry vision occurring weeks to months after surgery. These episodes may be accompanied by pain, photophobia, erythropsia, red eyes, anterior uveitis, and elevated intraocular pressure. However, complete loss of light perception is never observed. Diagnosis can be aided by the presence of microscopic hyphema during slit lamp examination. In some cases, there may be sufficient intraocular bleeding to cause a visible macroscopic hyphema without the need for a slit lamp. Additional features that may be observed include neovascularization of the iris or corneal edema, which occurs when the prolapsed intraocular lens comes into contact with the corneal endothelium. Gonioscopy can also be valuable in detecting blood in the trabecular meshwork between episodes[25]. Iris transillumination along the length of the haptic is a specific sign indicating chafing between the iris and IOL haptic[27]. However, diagnosing the location of the haptic can be challenging, and there are limited diagnostic imaging options available for this region of the eye. Different variations of UGH syndrome have been identified, including UGH Plus and Incomplete Posterior UGH (IPUGH). IPUGH is characterized by bleeding into the posterior chamber, with or without glaucoma, but without the presence of uveitis. On the other hand, UGH Plus refers to UGH syndrome accompanied by a vitreous hemorrhage and is more commonly observed in cases involving anterior chamber lenses with iris support. The loss of integrity of the anterior hyaloid, whether spontaneous, degenerative, or following surgery, creates a communication pathway between the aqueous humor and the vitreous, allowing for the passage of blood and the possibility of simultaneous bleeding in both chambers[27].

Treatment for UGH syndrome can be divided into two phases[25, 27]. The first phase focuses on managing symptoms during acute inflammation. This includes the use of topical steroid eye drops, such as 1% prednisolone acetate, to address uveitis at a frequency based on the severity of anterior chamber inflammation. Glaucoma can be managed through medications to reduce intraocular pressure, administered as eye drops, oral medications, or intravenous therapy depending on the severity of the condition. Hyphema can be managed by immobilization and head elevation to allow the blood in the anterior chamber to settle, along with the use of cycloplegic medication, such as 1% atropine, to prevent pupil movement and reduce pain from ciliary spasm.

The second phase of treatment involves managing chronic inflammation and addressing the underlying pathological cause of UGH syndrome. UGH syndrome is primarily caused by mechanical trauma to intraocular devices and ocular tissues, requiring surgical intervention to correct the underlying cause. In cases of mild inflammation, ophthalmologists may consider steroid eye drops and intraocular pressure control; however, surgical treatment options should be discussed with patients. The choice of surgery depends on the eye's pathology and may involve intraocular lens replacement, IOL repositioning, or other procedures such as vitrectomy with posterior capsulectomy to correct the mechanism causing UGH syndrome.

In conclusion, UGH syndrome arises from mechanical trauma to intraocular devices and ocular tissues, which used to be more common after cataract surgery with anterior chamber IOL insertion. However, advancements in artificial lens manufacturing technology and surgical techniques have changed its presentation. UGH syndrome is now primarily associated with posterior chamber IOLs placed in the sulcus or fixed to the sclera or iris. Ocular hypertension and vitreous hemorrhage are significant complications, and ultrasound biomicroscopy (UBM) is a valuable tool for understanding the pathogenesis, diagnosis, and treatment guidance. Treatment for

UGH syndrome involves two phases, targeting inflammation and reducing intraocular pressure, followed by addressing the underlying cause based on the specific pathogenesis mechanism, often requiring corrective surgery. A thorough understanding of the pathogenesis can help reduce the risk of UGH syndrome and prevent severe vision loss.

Chapter 3 Material and Methods

The study was conducted at King Chulalongkorn Memorial Hospital from June 2022 to May 2023 and performed under the approval of the Institutional Review Board (COA no. 0755/2022) and the tenets of the Declaration of Helsinki.

This study was not funded by a specific project grant.

Research design

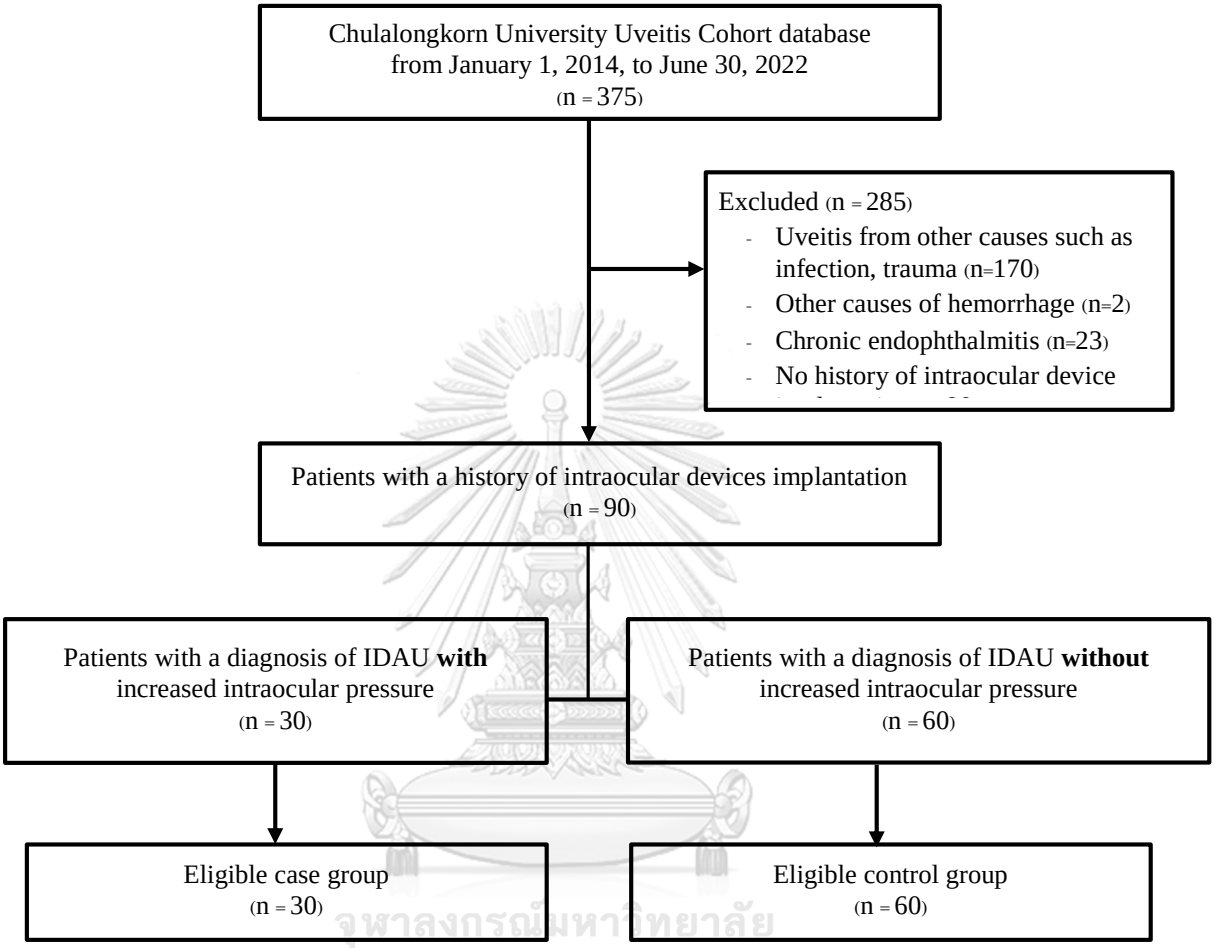
Retrospective, nested case control study

Research Methodology

Database and study cohort

We used the CU^2C database[7], which includes 375 patients who were followed up in a uveitis clinic in KCMH, Thailand, from 2014 to 2022. Cohort entry was defined as 1 August 2014 for all patients included in the study. The CU^2C database[7] contains records of all clinical information from outpatient visits, procedures, prescriptions, diagnosis records, and laboratory records from 1 August 2014 to 30 June 2022. We excluded the following patients from our study: (a) those diagnosed with uveitis from other causes, such as infection or trauma; (b) those diagnosed with other causes of hemorrhage, such as known retinal or choroidal pathology or trauma; (c) those diagnosed with chronic endophthalmitis; (d) those without a history of intraocular device implantation, and (e) those diagnosed with uveitis within 6 weeks after intraocular surgery (Figure 1). In summary, 30 subjects were included in the case group, and 60 subjects were included as controls. The present study was approved by the Institutional Review Board of The University of Chulalongkorn University (COA no. 0755/2022), which waived the requirement for patient informed consent due to the anonymous nature of the data. All methods were performed in accordance with the relevant guidelines and regulations.

Figure 1 Flow diagram of study cases and controls included in the data analysis. IDAU, intraocular device-associated uveitis.



Case and control definition

Case and control definitions were defined before data retrieval. Intraocular device-associated uveitis (IDAU) is a condition with IOL-iris contact from slit-lamp examination causing uveitis or intraocular hemorrhage. Cases and controls were participants from the CU^2C cohort database, KCMH, Chulalongkorn University which the recruitment period during 2014 to 2022.

Cases

Cases were defined as participants diagnosed with IDAU plus increased intraocular pressure (IOP > 21 mmHg).

Controls

Controls were participants who had clinical uveitis related to intraocular device implantation without increased IOP (≤ 21 mmHg).

Sample Size

Due to the exploratory nature of this study, no definite clear hypothesis, and the lack of prior studies on the topic, we were unable to conduct a formal sample size calculation. Instead, we relied on the available literature on UGH syndrome[6, 13, 17, 18], which mostly consisted of case series and case reports with sample sizes ranging from 10 to 30 cases. Based on this information, we determined that a sample size of 30 cases would be adequate for this study. However, it is important to note that this sample size may not be representative of the larger population of UGH syndrome patients, and our findings may be subject to limitations related to sample size and potential bias in the available literature. Nonetheless, we will ensure that our sampling strategy is well-defined and that our statistical analysis takes into account any potential limitations related to our sample size.

Research Tools

The instrument for this study is a structured questionnaire that modified from the questionnaire used at the CU^2C cohort database. The variables in the questionnaires are as follow:

1. General information of the study participants.
2. Information about clinical and laboratory investigation.

3. Information about the potential risk factors for increasing IOP: age, hypertension, high axial length, ruptured posterior capsule, transillumination iris defect, pseudophacodonesis, and malpositioned IOL
4. Information about treatment.

Data Collection

Retrieved from the data of the CU^2C cohort database

1. Cases were retrieved from the CU^2C cohort database which contained all name, diagnosis, and general information of participants of uveitis patient in KCMH. Then, investigators double-checked to make sure the person in question was identical in both the Cohort database and the medical record.
2. Following the retrieving of the confirmed cases, the controls were selected from those who have IDAU but not increased IOP.
3. Using ID of the cases and controls selected to retrieve the full questionnaires from CU^2C cohort database.
4. Fill the data of interest from the cohort study to the short questionnaire that was constructed by the investigators.

Data Management

All data was checked for accuracy and entered into the Microsoft Excel 2022 (Microsoft, Redmond, Washington, USA) for the analysis.

Study population and variables

All patients with uveitis with a history of intraocular device implantation in the CU^2C database[7] between 1 of August 2014 and 30 of June 2022 were included. The variables chosen for analysis are largely case series and case reports from a previous study[1, 2, 6, 11, 17, 21]. The potential factor variables were age, sex, comorbidities, long eye, myopia, vitrectomized eyes, ruptured posterior capsule, TID, malpositioned IOL, and single-piece IOL in sulcus.

Data Analysis and Statistics

Demographic data were analyzed using descriptive analysis, mean ± standard deviation (SD), median, frequency, and percentage as appropriate. Continuous and categorical variables were examined with Student's t test and Fisher's exact test, respectively, to test for differences between cases and controls. A logistic regression model was fitted with variables as potential factors using high intraocular pressure in IDAU as the main outcome variable (see Table 3). The odds ratio (OR) and its 95% confidence interval (95% CI) were calculated between cases and potential associated factors, including age, sex, comorbidities, long eye with axial length > 25 millimeters, myopia, vitrectomized eyes, ruptured posterior capsule, TID, malpositioned IOL, and single-piece IOL in the sulcus. The variables that were reported as significant factors were then selected for determination of the adjusted odds ratio (AOR) using the multivariate method. The presence of multiple collinearity was addressed before the analysis, and all variables indicated no collinearity. Analyses were carried out using IBM SPSS Statistics for Windows, version 23.0 (SPSS, Chicago, IL). P values less than 0.05 were considered statistically significant.

Chapter 4 Results

Participant demographics and clinical characteristics

The study flow chart describing patient recruitment is shown in Fig. 1. The general characteristics and clinical details of the patients and controls are presented in Table 2. In this study, there were 30 patients and 60 controls. The average age of the case group was 67.77±8.12 years, and 70% of them were women, while that of the control group was 49.15±11.30 years, and 58.3% were men. There was a statistically significant difference in age between the case and control groups (P=0.04). For sex, there was no statistically significant difference (P=0.28). Most comorbidities of case patients were hypertension (43.3%) and diabetes (36.7%), while those of the controls were diabetes (18.30%) and hypertension (16.70%). Compared to controls, case patients had a higher mean IOP (23.73±2.70 vs. 12.70±4.10). For the anatomical class of uveitis, both cases and controls had predominantly anterior uveitis (96.7% vs. 85%), followed by intermediate uveitis (0% vs. 5%) and panuveitis (3.3% vs. 10%). There was no statistically significant difference in the anatomical classes of uveitis between groups (P=0.20).

Table 2 Characteristics of the 30 case patients and the corresponding 60 controls included in the study.

	Case (n=30) N %	Control (n=60) N %	*P* Value
Age: mean (SD)	67.77 (8.12)	49.15 (11.30)	0.04
Sex			0.28
Male	9 (30%)	35 (58.3%)	
Female	21 (70%)	25 (47.7%)	
Comorbidities			
Hypertension	13 (43.3%)	10 (16.7%)	0.06
Diabetes	11 (36.7%)	11 (18.3%)	0.06
Myocardial infarction	4 (13.3%)	9 (15%)	0.83
Intraocular pressure: mean	23.73 (2.70)	12.70 (4.10)	0.04

(SD)			
Anatomical class of uveitis			0.20
Anterior uveitis	29 (96.7%)	51 (85%)	
Intermediate uveitis	0	3 (5%)	
Posterior uveitis	0	0	
Pan uveitis	1 (3.3%)	6 (10%)	

Clinical characteristics of intraocular device-associated uveitis with increased IOP

Anterior uveitis was the first clinical sign in all patients, followed by increased IOP. Two patients developed hyphema as the last clinical sign, followed by uveitis and increased IOP. There are two cases that require the surgical removal of the IOL and subsequent scleral fixation of a new IOL. Most of the complications were cystoid macular edema (13.33%), and posterior synechiae (3.33%). All cases of increased IOP were successfully treated with anti-glaucoma drugs.

Factors leading to high intraocular pressure in intraocular device-associated uveitis

Univariate and multivariate associations of factors leading to high IOP in IDAU are shown in Table 3. Univariate logistic regression analysis showed that age, hypertension, long eye (AL > 25 mm), ruptured posterior capsule, transillumination iris defect (TID), pseudophacodonesis, malpositioned IOL and single-piece IOL in the sulcus significantly increased the risk of increasing IOP among IDAU. Controlling for confounding with multivariate analysis illustrated that age (adjusted odds ratio (AOR) 1.18, 95% confidence interval (95% CI) 1.07–1.31, p = <0.002), long eye (AOR 8.08, 95% CI 1.18–55.16 p = 0.03) and IOL malposition (AOR 8.30, 95% CI 1.25–54.76; p = 0.03) significantly increased the risk of increasing IOP in IDAU (Figure 2).

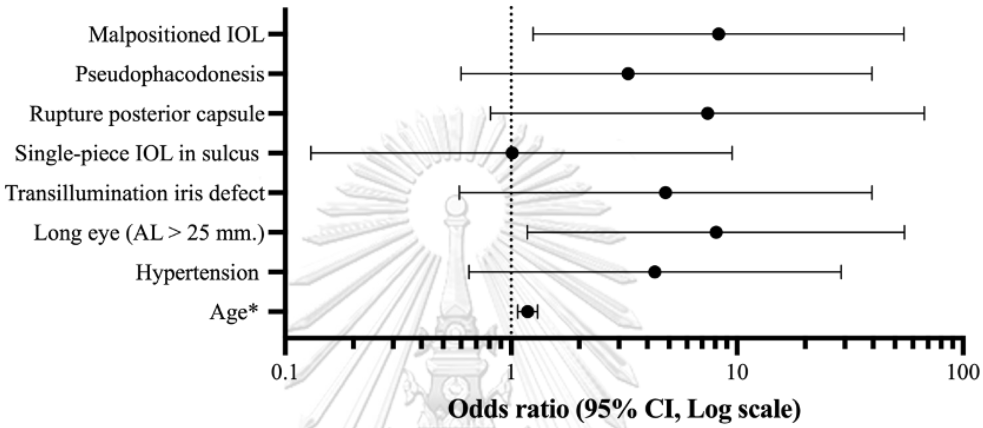
Table 3 Risk factors for increasing IOP in IDAU

	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Demographics				
Age	1.21 (1.12-1.31)	**<0.01**	1.18 (1.07-1.31)	**0.002**
Sex	1.67 (0.66-4.24)	0.28		
Comorbidities				
Hypertension	3.82 (1.42-10.30)	**0.01**	4.32 (0.65-28.90)	0.13
Diabetes	2.58 (0.96-6.94)	0.06		
Myocardial infarction	0.87 (0.25-3.10)	0.83		
Potential risk factors				
Long eye (AL > 25 mm)	3.78 (1.37-10.45)	**0.01**	8.08 (1.18-55.16)	**0.03**
Myopia	1.83 (0.75-4.47)	0.18		
Vitrectomized eye	1.00 (0.28-3.63)	1.00		
Rupture posterior capsule	3.25 (1.12-9.41)	**0.03**	7.40 (0.81-67.45)	0.08
Transillumination iris defect (TID)	3.78 (1.37-10.45)	**0.01**	4.82 (0.59-39.60)	0.14
Pseudophacodonesis	4.38 (1.48-12.95)	**<0.01**	3.29 (0.60-39.60)	0.22
Malpositioned IOL	9.94 (3.60-27.46)	**<0.01**	8.30 (1.25-54.76)	**0.03**
Single-piece IOL in sulcus	5.78 (1.37-24.32)	**0.02**	1.01 (0.13-9.50)	0.93

Notes, *P value □0.05 demonstrated the significance of regression analysis and appear in bold.

Figure 2 Forest plot showing odds ratios (ORs) for increasing IOP among IDAU patients after multivariate analysis.

The following variables were included in the multivariate model: age, hypertension, long eye, ruptured posterior capsule, TID, pseudophacodonesis, and malpositioned IOL. *Odds ratio per 1-year increment of age. IDAU, intraocular device associated uveitis; IOL, intraocular lens; AL, axial length



Chapter 5 Discussion and Conclusion

Uveitis-glaucoma-hyphema (UGH) syndrome is a rare condition and is commonly reported following anterior chamber IOL implantation or malposition posterior chamber IOL (PCIOL). The publications on UGH syndrome have been limited because of the extremely rarity of this condition. Recently, the incidence of UGH has significantly decreased due to advancements in cataract surgery technology, lens material and design, and the increasing trend of PCIOL[23]. On the other hand, there has been an increase in the prevalence of UGH caused by ocular devices other than IOLs, particularly in glaucoma device drainage (GDD) surgery. For instance, a case was reported in 2019 by Andrew Hou et al.[3] of UGH syndrome occurring after EX-PRESS shunt implantation, suggesting that UGH syndrome may become more prevalent with the use of new types of intraocular devices beyond IOLs. Another study by Armonaite et al.[2] in 2021 reported 71 patients with UGH syndrome, making it the largest retrospective study to date. They found that pseudophacodonesis was a risk factor for UGH syndrome, while blood thinners and transillumination iris defects were not specific to UGH syndrome.

In this study, we chose to use the term "intraocular device-associated uveitis" (IDAU) instead of UGH syndrome to encompass the broader clinical spectrum associated with this condition. IDAU can present with not only uveitis, glaucoma, and hyphema, but also with chronic inflammation, secondary iris neovascularization, pseudophacodonesis, transient intraocular pressure elevation, and cystoid macular edema[27]. We conducted a retrospective nested case-control study within a tertiary-based hospital setting to identify factors associated with increased intraocular pressure (IOP) in IDAU. Our findings showed that IOL malposition, long eye (axial length > 25 mm), and age were significantly associated with increased IOP in IDAU. Although not statistically significant, hypertension, rupture of the posterior capsule, transient intraocular pressure elevation, pseudophacodonesis, and the use of a single-piece IOL in the sulcus showed positive trends. IOL malposition was identified as the most

significant potential factor, with a 9-fold greater risk of increasing IOP in IDAU, while age had the lowest risk. In comparison to the controls, we found that each year of age was linked with a 1.2-fold increase in IOP in the IDAU. Our hypothesis is that older people may have a higher chance of zonule instability than younger people, resulting in increased iris-uveal contact. TID has been described as a feature of UGH syndrome in a number of previous studies [22, 28-31], but mostly in case reports. Some studies also reported that TID may not be a feature of UGH syndrome [9, 10].

Our study is the first study aiming to demonstrate the association between TID and increasing IOP in IDAU using a nested case control design, and our study's results confirm that TID was not associated with increasing IOP in IDAU. Recent studies[2] have demonstrated significant associations between an IOP 22 mmHg at the first time of intraocular hemorrhage and the subsequent need for IOP-lowering therapy in UGH syndrome. In the present study, we were unable to assess the relationship between IOP at the time of intraocular hemorrhage and the need for anti-glaucoma therapy in IDAU because only two patients with VH were observed in the case patient group. Since the malpositioned IOL was the factor that was most highly associated with increased IOP in our results, we emphasized that a meticulous slit-lamp exam postoperatively is necessary to confirm normal positioning of the IOL optic and haptics in the capsular bag. Each patient should be managed individually, taking into account potential risk factors (e.g., age, long eye), relative contraindications to a new intraocular surgery, and the patient's preferences. It is important to recognize IDAU as a rare complication that is associated with potentially serious morbidity, especially when accompanied by increasing IOP.

The strengths of the present study include that this is the first nested-case control study to investigate the association between potential risk factors and increasing IOP in IDAU. While most previous studies were case reports or descriptive findings, potential risk factor research using a tertiary cohort database has yet to be conducted.

The advantage of our nested case-control design was the reduction of selection bias, as both cases and controls were sampled from the same population. Additionally, information bias was minimized, as the assessment of risk factor exposure could be performed with the investigator blinded to the case status. Moreover, the potential for recall bias was minimized, as the examination of IOL position was a routine protocol followed by all doctors in the clinic. Second, both the cases and the controls were selected from the same population, reducing the possibility of selection bias. Finally, a retinal and uveitis expert documented and validated all patient and control information. The variables were also evaluated for collinearity and found to be unrelated.

Our work had some limitations. First, UGH or IDAU were clinically diagnosed and were diagnosed by many residents and fellows in the uveitis clinic. However, all cases were reviewed by the retina-uveitis specialist at the clinic. Similarly, since most of the patients were referred from other hospitals, the onset of clinical information was poorly recorded in the medical notes, for example, the date of uveitis onset or glaucoma or hyphema, so the exact date of some clinical findings could not be identified. Furthermore, we did not match patients with potential confounders because this is the primary exploratory study on the risk factor for elevated IOP in IDAU, and the definite confounder is yet unknown. Despite this, we tested all of the variables and saw no significant collinearity. Second, it is possible that the study was affected by misclassification bias. Patients may have been misdiagnosed with IDAU rather than viral-associated AU since the clinical presentation is similar, and we have not conducted anterior chamber paracentesis in all cases because it is too invasive, which may have overestimated the number of cases. Finally, as the number of cases in the analysis was available for only 30 patients due to the rarity of the disease, the 95% confidence intervals for the odds ratio of potential factors were broad. Despite these limitations, this study is valuable in providing previously unknown information that

may be utilized by retina or uveitis specialists, as well as general ophthalmologists, to enhance patient outcomes and preventive strategies in daily practice.

Conclusion

In this retrospective nested case–control study of intraocular device-associated uveitis, we found an association between potential risk factors, including IOL malposition, long eye (AL > 25), and age, and high IOP. Future work should incorporate host genetic, socioeconomic, and environmental factors to elucidate this association to inform future preventative strategies.

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https://www.aao.org/education/image/worm-in-eye-diffuse-unilateral-subacute-neuroretin

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