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China Glaucoma Treatment Pattern Study I–Primary Angle-Closure Glaucoma: protocol for a multicentre, retrospective, observational study

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ABSTRACT

Introduction Primary angle-closure glaucoma (PACG) is a leading cause of irreversible blindness globally, and the number of patients with PACG rises every year. Yet, there is a lack of knowledge about the clinical characteristics, therapeutic options and profile of patients with PACG in China. Hence, we design the China Glaucoma Treatment Pattern Study I–Primary Angle-Closure Glaucoma (Ch-GTP). The objective of this paper is to describe the design and methodology of Ch-GTP. The aim of this study is to characterise the profile and trend associated with initial PACG treatment for the last 10 years in China.

Methods Ch-GTP is a national multicentre retrospective observational study that will randomly sample from 50 hospitals throughout China. Over 7000 patient records hospitalised for initial PACG treatment from 2011 to 2020 will be selected randomly. The data from electronic medical records will be uploaded to an encrypted online platform that will receive and collate data from all collaborating hospitals. Data abstraction and monitoring will be performed in a standardised manner by trained statisticians to ensure consistency. Systematic data cleaning will also be conducted by statisticians to ensure data integrity before final data storage. The outcomes will include four broad categories: (1) demographics, (2) clinical characteristics, (3) therapeutic strategies and procedures and (4) early outcomes at discharge. The demographic characteristics and early outcomes will be summarised using descriptive statistics. Comparative analyses of characteristics and treatment pattern changing trends for different regions and years will be used to test for significant differences (t-test or Mann-Whitney U test).

Ethics and dissemination The collaborating hospitals obtained local approval based on a standard ethics application from internal ethics committees or acknowledged an existent ethics approval of the leading institution with approval from internal ethics committees. Due to the retrospective nature, written informed consent from patients was waived by the ethics committee. The results will be published in academic journals and presented at national and international academic conferences. Trial registration number ChiCTR2100054643.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The multicentre study will generate a nationally representative database and contribute new data regarding the profile and trend of initial primary angle-closure glaucoma treatment in China.
⇒ This study will involve various levels of hospitals to increase the representativeness and generalisability of the study findings.
⇒ As this is a retrospective observational design, this study will explore associations rather than causal relationships.
⇒ Data collection may be limited by information documented within the electronic medical records of hospitalised patients. Only early outcomes at discharge will be considered in this study.

INTRODUCTION

Glaucoma is a leading cause of irreversible blindness globally, with its population burden expected to grow from 60.5 million in 2011 to 111.8 million in 2040.1 2 Primary angle-closure glaucoma (PACG) is the most common glaucoma subtype that threatens binocular sight and is often referred to as more aggressive due to its higher rates of blindness.3 It has been estimated that about 5.9 million people were blinded for PACG worldwide in 2020.2 Besides, PACG is more prevalent in Asians than in other races, with 60% of PACG-induced blindness from East Asia.4 5 Specifically, the PACG prevalence was about twice that of primary open-angle glaucoma (POAG) in China.6 Considering per one-decade increase of life, PACG incidence doubles on average3; the simultaneous increase in life expectancy and PACG incidence is cause for concern and calls for this ocular disease to receive more attention.

The underlying strategy for treating PACG lies in reopening the angle between the iris...
Design and methodology of the Ch-GTP study will not focus on testing a specific hypothesis but on characterising and summarising the profile and trend of hospitalised patients with PACG in China. Actually, this study will not focus on testing a specific hypothesis but on characterising and summarising the profile and trend associated with initial PACG treatment.

With the population of PACG set to nearly double in 35 years and no widely recognised unifying management established in China, PACG has become a challenging public health challenge. The understanding of the clinical profile and treatment trends for patients with PACG in China may contribute to developing public health policy and specific pathways of eye health management, but the related data and studies are limited. Therefore, we design and plan to conduct the China Glaucoma Treatment Pattern Study I–Primary Angle-Closure Glaucoma (Ch-GTP) to generate results from a nationally representative database of hospitalised patients with PACG. Actually, this study will not focus on testing a specific hypothesis but on characterising and summarising the profile and trend associated with initial PACG treatment.

The specific aims of the Ch-GTP study are (1) to describe the profile of hospitalised patients with PACG in China, including demographic and clinical characteristics, therapeutic strategies and procedures, and early outcomes at discharge and (2) to compare the changes in these characteristics and initial treatment patterns for different regions and years. In this paper, we describe the design and methodology of the Ch-GTP study.

METHODS
Design overview
This multicentre retrospective observational study will extract data from the in-hospital electronic medical record (EMR) system during the past 10 years (from 1 January 2011 to 31 December 2020). The study will describe the clinical characteristics, therapeutic strategies and early outcomes at discharge of approximately 7800 patients with PACG undergoing initial treatment from 50 randomly sampled hospitals across China. Manual or electronic searches will retrieve all EMRs, with PACG as the primary diagnosis by the 10th Revision of International Classification of Diseases (ICD-10) codes, codes of diseases (GB/T 14396–2016) or discharge diagnosis terms if codes are unavailable.

Sampling design
The study subjects will be selected through a multistage stratified sampling method. According to the classification of the National Bureau of Statistics of China, the country consists of six geographical regions: North East, North China, North West, South West, South Central China and East China (Hong Kong, Macao and Taiwan are not included in the current study). One province will be randomly selected in each region, and two cities and four counties will be chosen randomly within each province. This study will select hospitals of various levels to reflect the diversity of PACG treatment in China. Two additional hospitals will be sampled randomly from the top 10 ophthalmic hospitals in China. Also, a university-affiliated hospital and a province-level people’s hospital will be non-randomly selected from each province. We will include a central hospital or a specialised eye hospital as the collaborating hospital in the selected cities or counties according to the area, as in-hospital treatment for PACG is mainly provided in the central hospital or a specialised eye hospital, which is the hospital with the best clinical capacity to treat PACG in the county. In total, 50 hospitals are expected to participate in this study.

Subsequently, we will select patients with PACG from the EMR database at each chosen collaborating hospital using systematic random sampling procedures, including routine hospitalisation or admission to day surgery. The number of cases to be selected per year will be allocated proportionately based on the total caseload per year in the collaborating hospital. We assume at least 300 patients will be enrolled at the provincial level or above hospitals in the study. With $\alpha$ at 0.05 (95% confidence level), the precision was evaluated for different estimates of frequency (figure 1) and is acceptable in the description of the treatment patterns and early outcomes. Given the size of hospitals and levels of medical care are different, the total admitted cases will vary. Therefore, the sample size will be adjusted for hospitals based on their caseload and catchment size. Figure 2 shows the relationship between the adjusted sample size and the total number of patients with PACG in the collaborating hospital. The sample size of each level will be determined according to calculated results and expert opinions. Consequently, with the aforementioned assumptions, the total expected sample volume is 7800 cases across 50 hospitals for the entire nation (table 1).
Study subjects
This study will collect a nationally representative sample of patients who received initial PACG treatment in the hospital. In China, most patients with PACG receive treatment during hospitalisation and have detailed records of hospitalisation. Therefore, all study subjects will consist of hospital admissions, who will be identified by retrieving and reviewing the medical records. PACG must be their primary diagnosis by an attending physician at discharge. The inclusion criteria will comprise the following: (1) the principal discharge diagnosis was PACG, and the primary purpose was to treat glaucoma; (2) age ≥ 18 years; and (3) data were entered into the EMR between 1 January 2011 and 31 December 2020. The exclusion criteria include (1) failure to complete treatment during hospitalisation, (2) active ocular and periocular infection or inflammation, (3) readmissions for high IOP after previous antiglaucoma surgeries, (4) POAG and (5) glaucoma secondary to penetrating keratoplasty, trauma, steroids, retinal disease/surgery, and neovascular or other diseases.

Main outcome measures
As the study’s primary aim is to describe the characteristics of patients with PACG and treatment in China, the outcomes from four broad categories will be collected from each participant: (1) demographics, (2) clinical characteristics, (3) therapeutic strategies and procedures, and (4) early outcomes at discharge (table 2).

<table>
<thead>
<tr>
<th>Grade of hospital</th>
<th>Sample size</th>
<th>Hospitals (n)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals from the top 10</td>
<td>300</td>
<td>2</td>
<td>600</td>
</tr>
<tr>
<td>University-affiliated hospital</td>
<td>300</td>
<td>6</td>
<td>1800</td>
</tr>
<tr>
<td>Hospitals from provincial-level cities</td>
<td>300</td>
<td>6</td>
<td>1800</td>
</tr>
<tr>
<td>Hospitals from city-level cities</td>
<td>150</td>
<td>12</td>
<td>1800</td>
</tr>
<tr>
<td>Hospitals from county-level cities</td>
<td>75</td>
<td>24</td>
<td>1800</td>
</tr>
<tr>
<td>Total</td>
<td>/</td>
<td>50</td>
<td>7800</td>
</tr>
</tbody>
</table>
of data entry errors. Senior investigators will supervise data entry and check at least 5% of the data independently.

**Data storage and management**
Systematic data cleaning and monitoring for the outlier, missing and improbable values will be checked before final data storage and will be carried out in collaboration with local hospital investigators. The processes will be performed and recorded according to standard procedures, and cleaned documents will include all scanned medical records. Patient privacy will be ensured by coding and anonymous processing by investigators, which will then be uploaded to an online data platform. After data cleaning and quality checks, this database will be kept secure in a locked and encrypted online database system. To protect the confidentiality of the data, an application

<table>
<thead>
<tr>
<th><strong>Category</strong></th>
<th><strong>Elements</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Age, sex, geographical location, grade of hospital and time to admission</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>Clinical diagnosis and stage, previous history of glaucoma or other diseases, previous ocular surgical history, medical history, number of antiglaucoma medications, ocular examination results (ie, UCVA, BCVA, IOP, AL, evaluation of the anterior chamber angle and lens and C:D)</td>
</tr>
<tr>
<td>Therapeutic strategies and procedures</td>
<td>Completion of examination (including gonioscopy, UBM, OCT, fundus photography, visual field examination and ocular biometry) (yes/no), set patient-specific target IOP (yes/no), completion of anterior chamber puncture (yes/no), the main therapeutic options, intrasurgical/postsurgical complications</td>
</tr>
<tr>
<td>Early outcomes at discharge</td>
<td>UCVA, BCVA, IOP, glaucoma medications, hospital length of stay</td>
</tr>
</tbody>
</table>

AL, axial length; BCVA, best-corrected visual acuity; C:D, cup/disc ratio; IOP, intraocular pressure; OCT, optical coherence tomography; UBM, ultrasound biomicroscope; UCVA, uncorrected visual acuity.

**Table 2**  China Glaucoma Treatment Pattern Study I—Primary Angle-Closure Glaucoma data elements

**Figure 3**  China Glaucoma Treatment Pattern Study I—Primary Angle-Closure Glaucoma flowchart of sampling, data collection, cleaning and analysis. PACG, primary angle-closure glaucoma.
form for obtaining data will be submitted in writing and signed for approval by the principal investigator and collaborating hospitals’ managers.

**Statistical analyses**

We will report the summary statistical results for patients with PACG in China over the past decade, including the clinical characteristics, ocular examinations completion rates, treatment options and early outcomes at discharge. Discontinuous variables will be expressed as a percentage (%) and continuous variables with normal distribution will be expressed as mean±SD. Variables not conforming to a normal distribution will be expressed as median values (IQRs). We will use standard parametrical techniques to analyse observational data, with all data assessed by two-sided tests. Continuous variables with a normal distribution will be compared using a two-sample t-test, and a two-sided Mann-Whitney U test will be used for data that is not normally distributed. Statistical significance will be defined when the p value is <0.05. Subgroup analysis will be performed based on age, sex, diagnosis, early outcomes and other factors. Potential factors influencing treatment and early outcomes will be modified by using multivariate logistic regression. Causal modelling methods for complex influencing factors will be considered if required. For missing values, statistical methods will impute or discard them, depending on the features and percentage of missing values. Analysis may be stratified based on the availability of data.

**Patient and public involvement**

Patients and the public are not involved in the design and conduct of this study.

**Ethics and dissemination**

The ethics committee approved this study protocol from the leading institution, the Eye Hospital, Wenzhou Medical University, in August 2021 (number 2021–126K-108-01). Depending on local needs and situations, the collaborating hospitals obtained local approval based on a standard ethics application from internal ethics committees or acknowledged an existing ethics approval of the leading institution with approval from internal ethics committees (online supplemental table 1). Due to the retrospective nature of the study, written informed consent from the patients was not required by the ethics committee. This study will not involve contact with patients. The main risk to participants is a potential leak of privacy, which will be minimised through the aforementioned data storage and management operational procedures. We will assign a unique study identification number to each case such that the uploaded medical records and final data will not contain any personally identifiable information. A data safety and monitoring board will review the study’s data safety regularly.

**Data sharing and dissemination**

Data and results will be shared among authors, but the leading institution (the Eye Hospital, Wenzhou Medical University) will be responsible for data integrity and statistical analysis. Participating investigators can request access to data for ancillary studies and be acknowledged as members of the ‘China Glaucoma Treatment Pattern Study Group’. The study results will be published in academic journals and presented at national and international conferences.

**DISCUSSION**

The risk of blindness and ageing in the Chinese population from PACG, coupled with unmatched treatment guidelines, threaten to burden healthcare services in China. Vision is critical to the quality of life and overall health; therefore, it is essential to reach a consensus on PACG guidelines for management to be established nationwide. Understanding the current status and needs is the first step for improvement. However, until now, no representative study has attempted to describe PACG treatment patterns in China on a national level.

Currently, therapeutic management for PACG varies substantially across geographical regions globally. In many countries, the treatment guidelines recommend that LPI be the first-line therapy for PACG. However, therapeutic guidelines for PACG differ in China. For example, patients presenting with PACG with peripheral anterior synchia (PAS) of >180° commonly receive Trab as an initial treatment, and LPI is only advocated if PAS is <180°. As the result of the EAGLE (effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma) study published, the theory regarding clear lens extraction as the initial treatment of PACG is becoming a new focus gradually. The EAGLE study has gained attention and interest in academia, but its impact on clinical practice remains unclear. However, no direct relevant data are available. Therefore, we hope to explore clinical patterns through the Ch-GTPI study.

As the data will be collected from all hospital types using a random sampling method, the Ch-GTPI study will generate a nationally representative sample of patients with PACG in China. Studies investigating this topic in the past have been single-centred and have used data from large academic tertiary hospitals in well-developed areas. There is a lack of emphasis on smaller, rural and regional hospitals about their therapies and outcomes. We anticipate that there are likely disparities in clinical characteristics, therapeutic strategies and early outcomes at discharge of patients with PACG in different Chinese regions, and the results will reveal the gaps in medical resources and treatment concepts among various areas and hospital types. These findings will have reference value for informing clinical guidelines and public health policymakers, for considering the needs of different patients and hospitals differently.

When conducting this study, we will establish an internet-based platform to complete data collection. This, combined with rigorous data quality control strategies, will ensure data quality. Given that each institution’s entry...
methods will strongly affect the data quality, on-site monitoring, regular checks and source document verification will ensure the integrity and authenticity of the data. This study will also use a criteria-based method to abstract data that will be standardised and supplemented with central training for all data abstractors to ensure consistency. The initial abstraction with poor internal consistency will be judged again by a senior reviewer. Moreover, investigators will source electronic or paper medical records for cases, which will be copied and transmitted in full after the deidentification of patient data. This ensures that as novel questions arise, further studies may be performed even if the additional data elements are not included in the initial case report forms. We hope these measures will translate to reliable findings which lay the foundation for future studies and offer an experience for other low-income countries.

The Ch-GTPI study has some limitations. First, as a retrospective observational study, these analysis results will explore association rather than causation, and hence all conclusions should be interpreted cautiously. Second, data sources are limited by documentation of the single hospitalisation visit in EMR and lack long-term follow-up. Thus, an assessment of the long-term effect cannot possibly be drawn for different treatment patterns. Third, in the screening process, using ICD codes to identify eligible patients may miss patients who meet eligibility criteria but were entered under an incorrect ICD code. Despite the probability of missing a small proportion of patients, this method is the most accurate, precise and practical, given the volume of data. We anticipate that only a very low number of patients will be missed, which is acceptable. Considering the limitations of this retrospective design, conducting a prospective study is warranted, which is currently being prepared and will detail the personal medical experiences and long-term outcomes of patients with PACG.

In conclusion, the Ch-GTPI study may be the first to extract a nationally representative sample from Chinese patients with PACG. The aims of the study are to characterise the clinical characteristics, therapeutic strategies and early outcomes at discharge in China. The clinical data after extraction and analysis will give a detailed understanding of patient characteristics and therapeutic trends in Chinese hospitals. Based on the understanding, the policy setters and healthcare providers could translate knowledge of the information of PACG into adjustments to their policies and medical decisions accordingly in order to improve care for patients. These findings would possess a certain reference value to future research and clinical work.

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Contributors Substantial contributions to the conception and design of the work: JC, XS, YZ, MH, and YL; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved: JC, JD, XX, DL, ZJ, YZ, DW, WG, JJ, GD, LT, ZW, PL, JM, XS, MH, YZ and YL; drafting the work or revising it critically for important intellectual content: JC, XS, MH and YL.

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