Characteristics and long-term outcomes of childhood glaucoma: a retrospective-cohort study [version 1; peer review: 1 approved, 2 not approved]

Supawan Surukrattanaskul¹, Pukkapol Suvannachart², Sunee Chansangpetch², Anita Manassakorn², Visanee Tantisevi², Prin Rojanapongpun²

¹Queen Sirikit National Institute of Child Health, Bangkok, Thailand
²Glaucoma Research Unit, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Abstract

Purpose: To evaluate the clinical characteristics and treatment outcomes of patients with childhood glaucoma.

Methods: We retrospectively reviewed the data of patients with childhood glaucoma who visited the glaucoma clinics at the Queen Sirikit National Institute of Child Health and the King Chulalongkorn Memorial Hospital between January 2008 and January 2018. The diagnosis was based on the Childhood Glaucoma Research Network classification. We recorded their clinical characteristics and requirement of any glaucoma interventions.

Results: A total of 691 eyes from 423 patients were included in this study. The patients predominantly comprised boys. The average follow-up duration was 71.3±63.8 months. The mean age at presentation was 3.9±4.4 years. Most patients presented with a high initial intraocular pressure (IOP) of 28.5±11.2 mmHg. Glaucoma associated with non-acquired ocular anomalies (22.9%) was the most common subtype, followed by primary congenital glaucoma (20.8%). We recorded a family history of glaucoma in 6.4% of patients. Most patients had bilateral glaucoma (63.4%) and required at least one intervention (51.5%). The average IOP at the latest follow-up visit was 19.1±10.8 mmHg. All glaucoma types had significantly lower IOP, compared to that at their baselines (all p<0.001). Moreover, most patients had an unfavourable visual acuity (49.5%) at their latest visit.

Conclusions: Secondary glaucoma associated with non-acquired ocular anomalies is the most common subtype of glaucoma. All subtypes, including primary glaucoma, were sporadic. The majority of patients had unfavourable visual outcomes. These real-world findings are fundamental to acquire a better understanding of childhood glaucoma.
glaucoma.

Keywords
care childhood glaucoma, congenital glaucoma, paediatric glaucoma,
Care Childhood Glaucoma Research Network classification, retrospective
care cohort, paediatric eye disease

Corresponding author: Sunee Chansangpetch (bae_sunnee@yahoo.co.uk)

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Introduction
Childhood glaucoma is a vision-threatening disorder with an incidence of 2.29 to 5.41 per 100,000 individuals\(^1\). The diagnosis of childhood glaucoma poses some challenges. This can be attributed to the variation in clinical presentations among different age groups. Despite high intraocular pressure (IOP) being the primary cause of glaucomatous damage, an accurate IOP measurement is not always obtained in children. Angle surgery is a common therapy but it is mostly associated with unfavourable outcomes in children, compared to that in adults\(^2\).

Childhood glaucoma encompasses several categories of glaucoma. The Childhood Glaucoma Research Network (CGRN) classification was proposed by an international consortium of glaucoma specialists in 2013 to standardise the definition of childhood glaucoma subtypes\(^3\). The prevalence of childhood glaucoma differs among ethnicities, ranging from 1:1,250 to 1:68,254 live births\(^4\). The incidence and clinical characteristics of childhood glaucoma in Thailand have not yet been reported. The Queen Sirikit National Institute of Child Health is one of the largest tertiary centres in Thailand. It is responsible for the treatment of a majority of the complex paediatric cases from all over the country. Paediatric glaucoma clinics have been established by the joint collaboration between the Queen Sirikit National Institute of Child Health and the King Chulalongkorn Memorial Hospital, a university-based hospital. These clinics aimed to treat all paediatric glaucoma cases that were referred to the aforementioned hospitals and have been operated by the same group of glaucoma specialists for more than 10 years. We aimed to describe the clinical characteristics and brief long-term treatment outcomes of the large paediatric glaucoma cohorts of the two major referral centres in Thailand.

Methods

Cohort selection
We retrospectively reviewed the medical records of all patients who had been examined at the paediatric glaucoma clinics of the Queen Sirikit National Institute of Child Health and the King Chulalongkorn Memorial Hospital between January 2008 and January 2018. The patient list was extracted from the hospital database to include all individuals that had at least one visit to the paediatric glaucoma clinic during the above period and/or subjects that had the ICD-10-CM diagnostic codes of Q15.0 and all H40 and H42 categories. The inclusion criteria were patients who aged <16 years at the time of the first clinic visit and met the CGRN definition of glaucoma or glaucoma suspect definition\(^4\). Cases with incomplete medical record precluding the diagnosis were excluded. The CGRN definition of glaucoma and suspected glaucoma has been previously described\(^4\).

Ethics approval
Ethical approval was obtained from the Research Ethic Committee of the Queen Sirikit National Institute of Child Health and Faculty of Medicine, Chulalongkorn University (REC.041/2562 and IRB.807/61). The requirement for written informed consent was waived due to the retrospective nature of the study.

Outcomes
We collected data for the demographic characteristics, initial clinical presentations, and diagnoses. All available clinical information was evaluated and classified according to the Childhood Glaucoma Research Network (CGRN) classification into the following seven groups: (1) primary congenital glaucoma (PCG), (2) juvenile open-angle glaucoma (JOAG), (3) secondary glaucoma following cataract surgery (SCG-C), (4) secondary glaucoma associated with non-acquired systemic disease or syndrome (SCG-S), (5) secondary glaucoma associated with non-acquired ocular anomalies (SCG-O); (6) secondary glaucoma associated with acquired conditions (SCG-A); and (7) glaucoma suspect (GS). The CGRN classification diagram has been illustrated elsewhere\(^5\).

We recorded the interventions during the follow-up course and final outcomes, including visual acuity (VA) and IOP at the latest available visit in eyes with a confirmed glaucoma diagnosis (diagnosis group 1 to 6). For glaucoma interventions, we reviewed the data to determine if the subjects had received any incisional surgeries (i.e. trabeculecctomy, trabeculotomy, and glaucoma drainage device implantation), cyclodestructive laser procedures (i.e. diode transscleral cyclophotocoagulation, diode laser endoscopic cyclophotocoagulation), or a combination of both at any time point of the follow-up period.

The best-corrected VAs were determined using the LEA or Snellen chart at 10 feet or 20 feet, respectively. In contrast, VA was graded by the fixation patterns using a central, steady, and maintained (CSM) technique for patients who were too young to determine the pictures or numbers\(^6\). The LEA chart symbols were reproduced with permission from Good-Lite Co., Elgin, IL. According to Karr et al., the fixation pattern of CSM, CSUM, CUSUM and UCUSUM was estimated as the VA of \(\geq\) 20/30, 20/30–20/100, \(\leq\)20/300, and \(\leq\)5/200, respectively. We extrapolated the Snellen acuity from the fixation grade with a modification from Karr et al.’s method and classified the VA into the following three groups: (1) favourable: best-corrected VA (BCVA) \(\geq\)20/70 or fixation grade of CSM, (2) moderately favourable: BCVA=20/70 to <20/400 or fixation grade of CSUM; and (3) unfavourable: BCVA<20/400 or fixation grade of CUSUM or UCUSUM.

Statistical analysis
The categorical data were presented as counts and percentages. We conducted the Shapiro-Wilk test for the normality of continuous data distribution. The data were reported as means and standard deviations or medians and interquartile ranges, depending on the distribution. We used the analysis of variance to compare the initial IOP among the glaucoma subtypes and the paired t-test to compare the IOP during the initial and latest visit. Furthermore, the Stuart-Maxwell test for marginal homogeneity was used to compare the proportion of matched pairs of the VA during the initial and latest visit. Statistical analyses were performed using Stata 13.0 (Stata Corp, College Station, TX, USA). A P-value \(<0.05\) was deemed statistically significant.
Results

The cohort comprised 423 patients (691 eyes). While 338 patients (532 eyes) were diagnosed with glaucoma, 85 patients (159 eyes) had GS. The average follow-up duration was 71.3±63.8 months (median 50; interquartile range, 22–112 months). Table 1 summarises the baseline characteristics. The average age at presentation was 3.91±4.40 years (median 1.75; interquartile range, 0.25–6.75 years). We recorded a family history of glaucoma in 15 (6.4%) patients. Furthermore, we found a statistically significant predominance of boys in all subjects (P=0.002), PCG (P=0.01), SCG-C (P=0.01), and GS (P=0.04). The mean of initial IOP was 28.5±11.2 mmHg. There was no difference in the initial IOP among the glaucoma subtypes (P=0.52). The most common presentation was cloudy eye (68.2%), which represented leukocoria or corneal haze, and megalocornea (14.5%). Table 2 demonstrates the mode of detection patterns and clinical presentations.

Most patients had bilateral glaucoma (63.4%). Among the 155 eyes of the unilateral cases, there were 72 (46.5%) and 83 (53.6%) right and left eyes, respectively. The diagnosis with significantly higher bilateral presentation included PCG (P=0.01), JOAG (P=0.03), SCG-O (P=0.03), and GS (P<0.001). SCG-S (unilateral 59.4%) and SCG-A (unilateral 53.6%) comprised a higher proportion of unilateral cases. However, the difference was statistically insignificant.

SCG-O was the most common subtype, accounting for 23% of the cohort or 29% of the glaucoma cases. In contrast, JOAG was the least common subtype. Figure 1 depicts the frequency of each glaucoma diagnosis.

The onset of PCG was neonatal (≤1 month), infantile (>1 to 24 months), and late (>2 years) in 33 (37.5%), 38 (43.2%), and two (2.3%) patients, respectively. However, the onset was undetermined in 15 (17.1%) patients with PCG. Figure 2 outlines the distribution of the anomalies associated with SCG-O, SCG-S, and SCG-A. We could obtain angle data for 56 eyes with SCG-A, of which 44 (78.6%) and 12 (21.4%) eyes had open and closed angles, respectively.

SCG-C was mostly observed following a surgery for a congenital idiopathic cataract (n=19, 57.6%), followed by congenital cataract associated with ocular anomalies or systemic diseases (n=7, 21.2%), and acquired cataract (n=3, 9.1%). There were four patients (12.1%) that the type of cataract could not be specified.

While 157 glaucomatous eyes (29.5%) underwent an incisional surgery, 68 eyes (12.8%) underwent a cyclodestructive laser surgery. In contrast, 49 (9.2%) eyes required both incisional and cyclodestructive procedures at any time point during the follow-up period. Figure 3 presents the frequency of glaucoma intervention in each glaucoma type.

SCG-A had the highest proportion of favourable VA at the initial (57.5%) and latest (53.4%) visits. However, JOAG had the highest proportion of unfavourable VA at the initial (53.9%) and latest (73.3%) visits. We observed a higher proportion of unfavourable VA at the latest visit in the overall glaucoma cases (P=0.03), compared to that at the initial visit. A worsening of the VA was primarily observed in the SCG-O group. Despite an approach in the shift, it failed to attain a statistical significance (P=0.07). Moreover, the average IOP was 19.1±10.8 mmHg at the latest visit. All glaucoma types had significantly lower IOPs, compared to the baseline values (all p<0.001). Table 3 shows a comparison of the VA and IOP between the initial and latest visits for each glaucoma type.

Conclusions/discussion

Childhood glaucoma comprises a group of eye disorders that affect children from their birth with a juvenile onset. Our study had an average follow-up of 6 years. SCG-O (22.9%) was the most common subtype, followed by PCG (20.8%) and SCG-A (18.9%). The condition mostly affected boys, with the majority being bilateral cases, similar to previously published results.

Primary glaucoma, both PCG and JOAG, and SCG-O commonly require at least one type of glaucoma intervention. Following the treatment, we observed significant IOP improvements in all subtypes. Nonetheless, half of the cases demonstrated unfavourable VA at the final visit.

Existing literature has reported on a varied distribution of the subtypes1,8–10,11. Most researchers have found a higher prevalence of secondary glaucoma, compared to primary glaucoma. However, reports from Canada8, Egypt, Great Britain and the Republic of Ireland1, and China1 have found that the majority of cases comprised PCG. The prevalence of secondary glaucoma depends on the prevalence of its aetiology (e.g. childhood cataract, hereditary systemic disease), which can differ among regions and ethnicities. Furthermore, this variation can be explained by the diagnostic criteria and study design. The diagnostic criteria of the studies conducted before 2013 were not based on the CGRN classification. In addition, hospital-based studies tend to have a higher proportion of complex cases, such as patients with syndromic and systemic involvement than those conducted in population-based settings. Table 4 summarises the distribution of childhood glaucoma according to the CGRN classification1,2,3,5–7,9,12.

Leukocoria or corneal haze were the leading presenting symptom in PCG (46.9%) and SCG-O (77%) similar with previous studies16–18. Moreover, most patients with JOAG were diagnosed without any symptoms. This could partially explain the most advanced stage at the time of diagnosis and the highest proportion of unfavourable VA outcomes in the aforementioned subtype. High IOP was the leading clue for glaucoma diagnosis. Furthermore, an enlarged corneal diameter was considered an important sign of PCG16.

We detected a family history of glaucoma in 6.4% of the 234 patients with an available family history. A study by Fung et al. reported on a family history of glaucoma in 17% patients with paediatric GS1. This high rate could be attributed to the
Table 1. Clinical and demographic characteristics of the study participants.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (423)</th>
<th>PCG (88)</th>
<th>JOAG (8)</th>
<th>SCG-C (33)</th>
<th>SCG-S (32)</th>
<th>SCG-O (97)</th>
<th>SCG-A (80)</th>
<th>GS (85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of eyes (patients)</td>
<td>691</td>
<td>145</td>
<td>15</td>
<td>54</td>
<td>45</td>
<td>156</td>
<td>117</td>
<td>159</td>
</tr>
<tr>
<td>Gender (patients, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>250 (59.1%)</td>
<td>56 (63.6%)</td>
<td>4 (50%)</td>
<td>24 (72.7%)</td>
<td>18 (56.3%)</td>
<td>53 (54.6%)</td>
<td>43 (53.8%)</td>
<td>52 (61.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>173 (40.9%)</td>
<td>32 (36.4%)</td>
<td>4 (50%)</td>
<td>9 (27.3%)</td>
<td>14 (43.8%)</td>
<td>44 (45.4%)</td>
<td>37 (46.3%)</td>
<td>33 (38.8%)</td>
</tr>
<tr>
<td>Age at presentation (years)</td>
<td>1.6 (0.3 to 6.8)</td>
<td>0.4 (0.2 to 4.4)</td>
<td>8.4 (5.3 to 12.4)</td>
<td>5.6 (1.8 to 7.6)</td>
<td>2.1 (0.4 to 6.3)</td>
<td>0.3 (0 to 3.0)</td>
<td>6.8 (2.8 to 10.4)</td>
<td>2.7 (0.6 to 7.7)</td>
</tr>
<tr>
<td>Family history (patients, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (6.4%)</td>
<td>0</td>
<td>1 (20.0%)</td>
<td>1 (7.7%)</td>
<td>2 (13.3%)</td>
<td>6 (10.7%)</td>
<td>0</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td>No</td>
<td>219 (93.6%)</td>
<td>35 (100%)</td>
<td>4 (80.0%)</td>
<td>12 (92.3%)</td>
<td>13 (86.7%)</td>
<td>50 (89.3%)</td>
<td>50 (100%)</td>
<td>55 (91.7%)</td>
</tr>
<tr>
<td>Laterality (patients, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>268 (63.4%)</td>
<td>57 (64.8%)</td>
<td>7 (87.5%)</td>
<td>21 (63.6%)</td>
<td>13 (40.6%)</td>
<td>59 (60.8%)</td>
<td>37 (46.3%)</td>
<td>74 (87.1%)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>155 (36.6%)</td>
<td>31 (35.2%)</td>
<td>1 (12.5%)</td>
<td>12 (36.4%)</td>
<td>19 (59.4%)</td>
<td>38 (39.2%)</td>
<td>43 (53.6%)</td>
<td>11 (12.9%)</td>
</tr>
<tr>
<td>Refraction (eyes, SE) †</td>
<td>0 (-2.00 to 1.25)</td>
<td>2.13 (2.13 to 2.13)</td>
<td>0</td>
<td>-2.25 (-6.63 to 5.50)</td>
<td>0.50 (0 to 1.25)</td>
<td>-2.88 (-3.25 to 3.00)</td>
<td>-1.25 (-2.00 to -0.25)</td>
<td>0.63 (-0.50 to 1.50)</td>
</tr>
<tr>
<td>Corneal diameter (eyes, mm)</td>
<td>11.5 (10 to 13)</td>
<td>12.5 (12 to 13)</td>
<td>10.5 (10 to 12)</td>
<td>10 (10 to 12)</td>
<td>11.5 (9 to 12.3)</td>
<td>11 (9 to 12.3)</td>
<td>11 (10 to 12)</td>
<td>11 (10 to 12)</td>
</tr>
<tr>
<td>Cup to disc ratio (eyes) ‡</td>
<td>0.6 (0.3 to 0.8)</td>
<td>0.8 (0.6 to 0.9)</td>
<td>0.9 (0.9 to 1.0)</td>
<td>0.4 (0.3 to 0.7)</td>
<td>0.5 (0.3 to 0.8)</td>
<td>0.3 (0.2 to 0.4)</td>
<td>0.4 (0.3 to 0.7)</td>
<td>0.6 (0.5 to 0.8)</td>
</tr>
</tbody>
</table>

Data shown in median (interquartile range).

* Data available in 234, 35, 13, 15, 56, 50, and 60 patients for total, PCG, JOAG, SCG-C, SCG-S, SCG-O, SCG-A, and GS, respectively.
† Data available in 93, 1, 2, 16, 5, 5, 19, and 45 eyes for total, PCG, JOAG, SCG-C, SCG-S, SCG-O, SCG-A, and GS, respectively.
‡ Data available in 426, 71, 14, 39, 34, 41, 71, and 156 eyes for total, PCG, JOAG, SCG-C, SCG-S, SCG-O, SCG-A, and GS, respectively.

IOP, intraocular pressure; SE, spherical equivalence; PCG, primary congenital glaucoma; JOAG, juvenile open angle glaucoma; SCG-C, secondary glaucoma following cataract surgery; SCG-S, secondary glaucoma associated with non-acquired systemic condition; SCG-O, secondary glaucoma associated with ocular anomalies; SCG-A, secondary glaucoma associated with acquired conditions; GS, glaucoma suspect.
Table 2. Mode of detection patterns in eyes with a glaucoma diagnosis.

<table>
<thead>
<tr>
<th>Mode of detection patterns</th>
<th>Total</th>
<th>PCG</th>
<th>JOAG</th>
<th>SCG-C</th>
<th>SCG-S</th>
<th>SCG-O</th>
<th>SCG-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presented with glaucoma-related symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cloudy eye</td>
<td>230 (69.1%)</td>
<td>68 (57.6%)</td>
<td>0</td>
<td>7 (100.0%)</td>
<td>9 (40.9%)</td>
<td>121 (85.8%)</td>
<td>25 (59.5%)</td>
</tr>
<tr>
<td>Megalocornea</td>
<td>49 (14.7%)</td>
<td>27 (22.9%)</td>
<td>0</td>
<td>0</td>
<td>10 (45.5%)</td>
<td>10 (7.1%)</td>
<td>2 (4.8%)</td>
</tr>
<tr>
<td>Epiphora</td>
<td>22 (6.6%)</td>
<td>13 (11.0%)</td>
<td>0</td>
<td>0</td>
<td>2 (9.1%)</td>
<td>6 (4.3%)</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>Red eye</td>
<td>14 (4.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (4.5%)</td>
<td>4 (2.8%)</td>
<td>9 (21.4%)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>13 (3.9%)</td>
<td>9 (7.6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (9.5%)</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>2 (0.6%)</td>
<td>1 (0.9%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>3 (0.9%)</td>
<td>3 (100.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>From clinical surveillance or screening (no glaucoma-specific symptoms) *</td>
<td>126</td>
<td>-</td>
<td>6</td>
<td>32</td>
<td>17</td>
<td>9</td>
<td>62</td>
</tr>
<tr>
<td>Unknown / missing data</td>
<td>73</td>
<td>27</td>
<td>6</td>
<td>15</td>
<td>6</td>
<td>6</td>
<td>13</td>
</tr>
</tbody>
</table>

Data shown in number of eyes (%).

* Including eyes from clinical surveillance in known systemic or ocular diseases, clinical surveillance due to family history of glaucoma and other forms of child health screening.

PCG, primary congenital glaucoma; JOAG, juvenile open angle glaucoma; SCG-C, secondary glaucoma following cataract surgery; SCG-S, secondary glaucoma associated with non-acquired systemic condition; SCG-O, secondary glaucoma associated with ocular anomalies; SCG-A, secondary glaucoma associated with acquired conditions.

Figure 1. Subtypes of childhood glaucoma. PCG, primary congenital glaucoma; JOAG, juvenile open angle glaucoma; SCG-C, secondary glaucoma following cataract surgery; SCG-S, secondary glaucoma associated with non-acquired systemic condition; SCG-O, secondary glaucoma associated with ocular anomalies; SCG-A, secondary glaucoma associated with acquired conditions; GS, glaucoma suspect.

tendency of having the eyes checked because of a family history of glaucoma. In our study, an exclusion of the GS cases would have reduced the rate of positive family history from 6.4% to only 5.7% (10 out of 174 patients). This value was half of that reported by Papadopoulos et al. (11%)². Despite the association of PCG and JOAG with certain mutations¹⁹, our
Figure 2. Causes of secondary glaucoma subtypes that are associated with non-acquired systemic disease, non-acquired ocular anomalies, and acquired conditions.
cohort revealed a positive family history in none of the PCG cases and in only one JOAG case. Therefore, the PCG cases in Thailand were sporadic rather than inherited.

In line with the published literature, we found that surgical interventions were mostly required in the primary type of glaucoma, both PCG and JOAG. Moreover, medication was the mainstay of treatment for most secondary glaucoma cases. In addition, SCG-O cases reported a high rate of surgical intervention. The pathology of the above-mentioned subtype is related to angle dysgenesis, which usually makes it difficult to control the disease.

Ramkrishanan et al. reported a significant improvement of VA, which was sustained for at least four years of follow-up. This was in contrast to the marginally significant worsening of VA observed in our study. This disparity could be attributed to a greater proportion of PCG cases in the study conducted by Ramkrishanan et al. The improvement of VA in their study was attributed to an improved corneal clarity following surgery.

We found that the SCG-A cases had the most favourable VA at the latest visit and the best initial VA. The majority of the cases included steroid-induced glaucoma, which might be more controllable than the subtypes related to congenital ocular malformations, such as PCG and SCG-O. However, we found an overall worse VA, compared to that reported in previous publications. This discrepancy could be explained by the following aspects. First, we documented a high proportion of unfavourable VA during the initial visits. Khitri et al. reported on an association between poor vision at diagnosis and visual impairment (<20/200). Second, our cases were diagnosed at an extremely young age, particularly in the PCG (median age 0.5 years) and SCG-O (median age 0.3 years) groups. Studies on the PCG subtype reported on final VA <20/200 in children diagnosed before the age of three months regardless of their IOP levels. It was hypothesised that the earlier presentation reflected the poorer development of the angle. In other words, the disease was more severe. Nevertheless, the study design and definition of unfavourable VA differed among the studies.

Our study had the strength of being a large cohort study with a long follow-up duration. Our data also represents the majority of childhood glaucoma cases in Thailand. However, it had several limitations. First, there were some incomplete...
Table 3. Visual acuity and intraocular pressure in eyes with a glaucoma diagnosis.

<table>
<thead>
<tr>
<th>Follow up period (months) median (IQR)</th>
<th>Initial visual acuity N (%)</th>
<th>Last visual acuity N (%)</th>
<th>P value*</th>
<th>Initial intraocular pressure (mmHg) mean (SE)</th>
<th>Last intraocular pressure (mmHg) mean (SE)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Favorable</td>
<td>Moderately favorable</td>
<td>Unfavorable</td>
<td>Favorable</td>
<td>Moderately favorable</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>All glaucoma</td>
<td>60 (27 to 122)</td>
<td>103 (39.0%)</td>
<td>58 (22.0%)</td>
<td>103 (39.0%)</td>
<td>140 (34.7%)</td>
<td>64 (15.8%)</td>
</tr>
<tr>
<td>PCG</td>
<td>83 (36 to 134)</td>
<td>14 (24.6%)</td>
<td>14 (24.6%)</td>
<td>29 (50.9%)</td>
<td>30 (28.9%)</td>
<td>16 (15.4%)</td>
</tr>
<tr>
<td>JOAG</td>
<td>96 (15 to 156)</td>
<td>4 (30.8%)</td>
<td>2 (15.4%)</td>
<td>7 (53.9%)</td>
<td>3 (20.0%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>SCG-C</td>
<td>47.5 (25 to 114)</td>
<td>12 (28.6%)</td>
<td>17 (40.5%)</td>
<td>13 (31.0%)</td>
<td>17 (34.0%)</td>
<td>18 (36.0%)</td>
</tr>
<tr>
<td>SCG-S</td>
<td>57 (27 to 111)</td>
<td>6 (30.0%)</td>
<td>10 (50.0%)</td>
<td>4 (20.0%)</td>
<td>13 (46.4%)</td>
<td>7 (25.0%)</td>
</tr>
<tr>
<td>SCG-O</td>
<td>75 (40 to 138)</td>
<td>17 (37.8%)</td>
<td>7 (15.6%)</td>
<td>21 (46.7%)</td>
<td>22 (21.2%)</td>
<td>16 (15.4%)</td>
</tr>
<tr>
<td>SCG-A</td>
<td>38 (16 to 81)</td>
<td>50 (57.5%)</td>
<td>8 (9.2%)</td>
<td>29 (33.3%)</td>
<td>55 (53.4%)</td>
<td>6 (5.8%)</td>
</tr>
</tbody>
</table>

* Calculated from the paired data of eyes with available initial visual acuity and latest visual acuity- all glaucoma 253 pairs, PCG 53 pairs, JOAG 13 pairs, SCG-C 42 pairs, SCG-S 17, SCG-O 41 pairs, and SCG-A 87 pairs.

† Calculated from the paired data of eyes with available initial intraocular pressure and latest intraocular pressure- all glaucoma 634 pairs, PCG 129 pairs, JOAG 14 pairs, SCG-C 53 pairs, SCG-S 41, SCG-O 139 pairs, and SCG-A 110 pairs.

PCG, primary congenital glaucoma; JOAG, juvenile open angle glaucoma; SCG-C, secondary glaucoma following cataract surgery; SCG-S, secondary glaucoma associated with non-acquired systemic condition; SCG-O, secondary glaucoma associated with ocular anomalies; SCG-A, secondary glaucoma associated with acquired conditions.
Table 4. Distribution of childhood glaucoma according to the Childhood Glaucoma Research Network classification.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of glaucoma patients</th>
<th>Population</th>
<th>PCG</th>
<th>JOAG</th>
<th>SCG-C</th>
<th>SCG-S</th>
<th>SCG-O</th>
<th>SCG-A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital-based setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current study</td>
<td>338</td>
<td>2 Tertiary paediatric glaucoma clinics, Thailand</td>
<td>88 (26%)</td>
<td>8 (2.4%)</td>
<td>33 (9.8%)</td>
<td>32 (9.5%)</td>
<td>97 (28.7%)</td>
<td>80 (23.6%)</td>
</tr>
<tr>
<td>Senthil <em>et al.</em> 2019</td>
<td>275</td>
<td>Tertiary eye care, India</td>
<td>107 (38.9%)</td>
<td>38 (13.8%)</td>
<td>22 (8%)</td>
<td>16 (5.8%)</td>
<td>48 (17.5%)</td>
<td>44 (16%)</td>
</tr>
<tr>
<td>Mokbel <em>et al.</em> 2018</td>
<td>207</td>
<td>Chief referral center, Egypt</td>
<td>114 (55%)</td>
<td>2 (1%)</td>
<td>15 (7.2%)</td>
<td>4 (2%)</td>
<td>11 (5.3%)</td>
<td>61 (29.5%)</td>
</tr>
<tr>
<td>Hogue <em>et al.</em> 2016</td>
<td>122</td>
<td>Tertiary childhood glaucoma clinic, USA</td>
<td>39 (32%)</td>
<td>9 (7.4%)</td>
<td>22 (18%)</td>
<td>14 (11.5%)</td>
<td>10 (8.2%)</td>
<td>28 (22.9%)</td>
</tr>
<tr>
<td>Fung <em>et al.</em> 2013</td>
<td>152</td>
<td>Dallas Glaucoma Registry, USA</td>
<td>46 (30.3%)</td>
<td>10 (6.6%)</td>
<td>30 (19.7%)</td>
<td>18 (11.8%)</td>
<td>16 (10.5%)</td>
<td>32 (21.1%)</td>
</tr>
<tr>
<td>Qiao <em>et al.</em> 2009†</td>
<td>948</td>
<td>Hospitalized paediatric patients, Beijing, China</td>
<td>486 (51.3%)</td>
<td>63 (6.6%)</td>
<td>125 (13.2%)</td>
<td>40 (4.2%)</td>
<td>61 (6.4%)</td>
<td>173 (18.3%)</td>
</tr>
<tr>
<td>Taylor <em>et al.</em> 1999†</td>
<td>296*</td>
<td>Hospital for sick children, Toronto, Canada</td>
<td>117 (39.5%)</td>
<td>7 (2.4%)</td>
<td>61 (20.6%)</td>
<td>32 (10.8%)</td>
<td>38 (12.8%)</td>
<td>41 (13.9%)</td>
</tr>
<tr>
<td>Barsoum-Homsy <em>et al.</em> 1986</td>
<td>63</td>
<td>Paediatric glaucoma clinic, Montreal, Canada</td>
<td>14 (22.2%)</td>
<td>0</td>
<td>7 (11.1%)</td>
<td>9 (14.2%)</td>
<td>24 (38%)</td>
<td>9 (14.2%)</td>
</tr>
<tr>
<td><strong>Population-based setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aponte <em>et al.</em> 2010†</td>
<td>30</td>
<td>Olmstead county residents, Minnesota, USA</td>
<td>1 (3.3%)</td>
<td>4 (13.3%)</td>
<td>6 (20%)</td>
<td>4 (13.4%)</td>
<td>2 (6.7%)</td>
<td>13 (43.3%)</td>
</tr>
<tr>
<td>Papadopoulos <em>et al.</em> 2007</td>
<td>91*</td>
<td>British Ophthalmic Surveillance Unit, Great Britain and Republic of Ireland</td>
<td>45 (49.4%)</td>
<td>2 (2.2%)</td>
<td>16 (17.6%)</td>
<td>12 (13.2%)</td>
<td>6 (6.6%)</td>
<td>10 (11%)</td>
</tr>
</tbody>
</table>

* We excluded patients who were glaucoma suspect or had an unknown diagnosis.
† The diagnosis was reclassified from the original articles to follow the CGRN classification.

PCG, primary congenital glaucoma; JOAG, juvenile open angle glaucoma; SCG-C, secondary glaucoma following cataract surgery; SCG-S, secondary glaucoma associated with non-acquired systemic condition; SCG-O, secondary glaucoma associated with ocular anomalies; SCG-A, secondary glaucoma associated with acquired conditions.
data because of the retrospective design. Moreover, information on some clinical examinations, such as VA and IOP could not always be obtained in children at every clinic visit. Second, the long follow-up period resulted in a shift in the IOP measurement methods from a handheld contact tonometer (Tono-Pen; Reichert, New York, USA) to a rebound tonometer (iCare TA01i, Tiotat Oy, Helsinki, Finland) in extremely young or non-cooperative children. Third, there was inadequate information to clearly identify the cause of unfavourable VA outcomes. Future research should explore this underlying issue.

In conclusion, data from the referral centres in Thailand showed a higher prevalence of secondary glaucoma than primary glaucoma. Using the CGRN classification, secondary glaucoma associated with non-acquired ocular anomalies was found to be the most common subtype. All subtypes, including primary glaucoma, were sporadic. A majority of the cases had unfavourable visual outcomes. These real-world findings are fundamental data and provide a better understanding of childhood glaucoma.

**Data availability**

Underlying data

Harvard Dataverse: Childhood glaucoma, https://doi.org/10.7910/DVN/V3HFN

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

**References**

This interesting study analyzed the clinical characteristics and treatment results of patients with childhood glaucoma who had visited the glaucoma clinics at the Queen Sirikit National Institute of Child Health and the King Chulalongkorn Memorial Hospital within 10 years, and provided effective data and analysis for a better understanding of children's glaucoma in Thailand. There are several questions that need to be answered:

1. In the "Results" of the "Abstract", "Most patients presented with a high initial intraocular pressure (IOP) of 28.5±11.2 mmHg." Does the patients here refer to all patients or just for the patients with a high initial IOP?

2. In the "Results", you described that “The average age at presentation was 3.91±4.40 years (median 1.75: interquartile range, 0.25–6.75 years).” But in the “Table 1”, the average age at presentation of the total patients is 1.6(0.3 to 6.8) years. Please give a more detailed explanation here or check data again.

3. In this study, the authors only collected the family history of 234 of the 423 patients, as you described that “We detected a family history of glaucoma in 6.4% of the 234 patients with an available family history.” in the “Conclusions/discussion”. We suggest that the description of this in the previous part “Result” that “We recorded a family history of glaucoma in 15 (6.4%) patients” need to be added the information that the data was from 234 patients, so as not to cause misleading or doubt. Besides, when analyzing the family history of patients, the author did not analyze the fact that the family history of not all the patients had been collected. This will inevitably lead to a certain degree of bias. Without analyzing this, the conclusion that“ Therefore, the PCG cases in Thailand were sporadic rather than inherited.” could be not that reliable.

4. There are several places in the article that need to be supported by the literature: a） In the “Conclusion” that “The condition mostly affected boys, with the majority being bilateral cases, similar to previously published results.”b） In the “Conclusion” that “In addition, SCG-O cases reported a high rate of surgical intervention.”
5. In the “Conclusion”, you described that “This disparity could be attributed to a greater proportion of PCG cases in the study conducted by Ramkrishanan et al.” Please please provide the PCG ratio of this research and the comparison with that of your study to compare the difference between the two more intuitively.

6. In the description SCG-A had the most favourable VA at the latest visit and the best initial VA, you described that “The majority of the cases included steroid-induced glaucoma, which might be more controllable than the subtypes related to congenital ocular malformations, such as PCG and SCG-O.” But from Figure 2, steroid-induced glaucoma accounts for 29%, which is not so high. Does the authors mean “The majority of the cases such as steroid-induced glaucoma, which might be more controllable than the subtypes related to congenital ocular malformations...”?

Is the work clearly and accurately presented and does it cite the current literature? Yes

Is the study design appropriate and is the work technically sound? Yes

Are sufficient details of methods and analysis provided to allow replication by others? Yes

If applicable, is the statistical analysis and its interpretation appropriate? Partly

Are all the source data underlying the results available to ensure full reproducibility? Yes

Are the conclusions drawn adequately supported by the results? Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Glaucoma

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
This article successfully reports the clinical characteristics and treatment outcomes of patients with childhood glaucoma from the real-world large data of 10 years in Thailand.

The statistics used are appropriate and the interpretations are consistent. Overall findings in this study are important to the field. However, there are a few points need to be fixed, and discussion needs more work to improve the interpretation of the results.

Major comments:
1. The discussion about the reason of unfavorable visual outcome is insufficient. Authors should dig much deeper into the reason of visual impairment of their patients, whether it was really unavoidable or not.
   For example, JOAG group mainly seems to have clear cornea where disc is visible (14/15) and good IOP control (25.6 to 15.0 mmHg), however, the unfavorable cases were increasing compared to the initial VA. What caused the unwilling visual outcome?
   Is it due to the corneal haziness or glaucoma progression? Inadequate orthoptic exercises? Or merely gathering of very severe cases to the tertiary hospitals?
   If there are any possible clues or suggestions to improve, it might be a good help for the readers who are struggling under the same situation.

2. As the authors mentioned, surgical interventions were mostly required in the primary type of glaucoma, both PCG and JOAG, and especially SCG-O. However, from this study, no glaucoma intervention was performed to 46.7, and 42.3% of the patients of JOAG and SCG-O, respectively. Explain the reason why almost a half of the patients did not need the surgical intervention.

Minor comments:
1. Need the details of surgical procedures.

2. Are there any relations between the laterality and visual outcome?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** glaucoma

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 15 March 2021

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**Chungkwon Yoo**
Department of Ophthalmology, Korea University College of Medicine, Seoul, South Korea

The authors evaluated the clinical characteristics and treatment outcomes of patients with childhood glaucoma seen in their glaucoma clinics for 10 years. This is a clinically interesting study. However, there are some issues which need to be addressed.

1. Please add the specific information on the surgical interventions used and their proportions in each glaucoma subtype: trabeculectomy, goniotomy, trabeculotomy or tube surgery?

2. Corneal diameters at initial visit?

3. Poor VA outcome may have resulted from factors other than glaucoma..e.g. inadequately corrected VA or coexisting eye problems. How many of the study eyes had been seen by pediatric ophthalmologists?

4. You may analyze the factors associated with poor visual outcome.

5. Given the fact that PCG needs surgical management, the proportion of nonsurgically managed eyes among PCG cases was unexpectedly high. What were the reasons for nonsurgical management in those patients? Please address this issue in the discussion section.

6. The authors concluded that all subtypes of glaucoma were sporadic. Although the patient-reported or family-reported ‘family history of glaucoma’ was uncommon, the actual familial occurrence may be more than can be assessed by history taking. Unless each family member was examined for glaucoma, you may not be certain that all subtypes of childhood
glaucoma were sporadic.

**Is the work clearly and accurately presented and does it cite the current literature?**
Yes

**Is the study design appropriate and is the work technically sound?**
Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**
Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**
Yes

**Are all the source data underlying the results available to ensure full reproducibility?**
Yes

**Are the conclusions drawn adequately supported by the results?**
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** glaucoma surgery

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.