world, as well as in Japan [4, 5]. The value of cataract surgery is firmly established, and as a result, cataracts account for approximately one-third of medical spending on eye care [6]. As the Japanese population ages, the prevalence of visual impairment is projected to increase from 1.35% of the population in 2007 to 2.0% by 2050 [7]; hence, visual impairment resulting from cataracts is on the rise. Therefore, an important challenge is to assess the cost-effectiveness of cataract surgery.

A cost-effectiveness study that uses the concepts of utility and quality-adjusted life-years (QALYs), in which the quantity of life is combined with the quality of life (QOL), is termed a cost-utility analysis. Several previous studies have assessed the cost-utility of cataract surgery [8–13]. In the US, Busbee et al. [8] reported that the cost-utility of first eye cataract surgery was $2,020/QALY and concluded that initial cataract surgery was highly cost-effective when compared with procedures across multiple medical specialties. In Sweden, Kobelt et al. [9] estimated the cost-utility of cataract surgery in one eye as US $4,500/QALY, and a recent systematic review to determine the cost-effectiveness of cataract surgery concluded that it is a cost-effective procedure by any measure in the Western world [11]. To confirm the generalizability of the cost-utility of cataract surgery in the real-world setting in Japan, we conducted a multicenter study based on data from 12 clinical sites in Japan.

Participants and methods

This study was a prospective multicenter observational study conducted by the Eye Care Comparative Effectiveness Research Team (ECCERT) at 12 clinical sites in Japan (see Appendix). A prospective observational protocol was developed by ECCERT to evaluate visual and patient-reported outcomes before and after routine cataract surgery. Seven ophthalmologic departments in university hospitals, three ophthalmologic departments in public hospitals, and two private surgical clinics were recruited; all agreed to participate in the study. The study protocol was approved by the institutional review board of each facility, and the conduct of the study followed the tenets of the Declaration of Helsinki.

Study population

Patients were eligible for inclusion in the study if they were scheduled for first eye, second eye, or bilateral cataract surgery, and were aged 50 years or older. Patients were excluded if the planned cataract surgery was a combined procedure involving glaucoma, corneal, or vitreoretinal surgery. Further exclusions were made if patients had any visually significant coexisting ocular pathology, such as macular diseases, glaucoma, optic atrophy, amblyopia, and proliferative diabetic retinopathy with dementia, or were unwilling or unable to respond to the complex questions. Each participant gave written informed consent to participate in this study. Patients were recruited from 1 November 2008 through 28 February 2010. A total of 549 patients were initially registered.

A full preoperative medical history and an ophthalmic examination for each patient were obtained. The ophthalmic examination included visual acuity, types of cataract (nuclear, cortical, or posterior subcapsular cataract), and presence of any other ocular disease. The visual acuity was reported as a corrected decimal acuity obtained according to the usual routine of each clinic. The ophthalmologist who performed the examination reported the results using a structured data sheet. Intraoperative techniques, complications, and 3-month clinical outcomes were also reported by the treating ophthalmologist. All patients were asked whether they had a history of systemic comorbidities, including cardiovascular diseases (hypertension, angina, heart failure, myocardial infarction, use of a pacemaker), cancer, diabetes, renal and hepatic diseases, gastrointestinal diseases (gastric ulcer, enteritis, colitis), respiratory diseases, musculoskeletal diseases (rheumatoid arthritis, spinal disorder), neurological diseases (paralysis such as stroke, need for ambulatory assistance), and deafness or hearing impairment.

Utilities assessment

Prospective assessment of patient preference-based QOL (utility) was performed before and after the surgery. In health economic analysis, utility is defined on a continuous scale from 0 to 1, where 0 corresponds to the worst possible QOL weight (equal to death) and 1 corresponds to the best possible QOL weight (equal to perfect health). The patient preference-based time tradeoff (TTO) method was used in this study [14]. Each patient was interviewed preoperatively by trained interviewers, not by the attending ophthalmologists. All the interviewers in the participating clinics had completed the training workshop, and utility values were obtained by them in an agreed-upon fashion using the same questionnaire and the standard technique of each facility. The patient was asked if he/she would be willing to trade a certain portion of his/her remaining life, from a life expectancy of 20 years, in return for being rid of visual impairment and all its associated effects under these hypothetical conditions. Time tradeoff utility was calculated according to the following equation: utility = $1 - x/20$ (x = years of life he/she would be willing to give up). Out of the 12 clinical sites, 1 site could not conduct the TTO interview; therefore, results from questionnaires completed by 440 patients from 11 clinical sites were included in the TTO analysis at baseline.

Information for other utility assessments was collected from the patients by means of survey questionnaires. The questionnaires consisted of the Japanese versions of the EuroQol (EQ5D) [15, 16] and the Health Utility Index Mark 3 (HUI3) [17, 18]. The EQ5D comprises 5 questions that measure 5 health concepts (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with 3 levels of answers leading to 243 possible combinations of answers describing a different health status between 1 (= perfect health) and −0.063 (a health status that can be considered worse than death). The HUI3 comprises 15 questions addressing 8 health attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain) and 1 question that measures overall self-assessed health status. A weighted-scoring algorithm is applied to combine the scores of each attribute to derive a value between 0 and 1 to represent utility of the overall health state (perfect health = 1, deceased = 0). These questionnaires were collected from the 12 clinical sites; however, because of inability to collect survey forms and no method to account for the missing values, we were able to obtain answers from only 541 patients for the EQ5D and 496 patients for the HUI3 at baseline. The patients were encouraged to complete the follow-up questionnaires, which included the TTO, EQ5D, and HUI3 questionnaires, mailed to their homes 3 months after the surgery, and to return them by post. Later, however, for reasons including withdrawal of consent, insufficient information on clinical findings from the responsible physicians, and inability to collect survey forms from patients, we were able to obtain complete information on only 381 patients for the TTO method, 482 patients for the EQ5D, and 434 patients for the HUI3.

Cost-utility analysis

The cost estimates for this study included only direct costs. All medical costs are uniformly standardized by the social medical insurance system in Japan. The medical costs associated with cataract surgery were calculated based on the Japanese social insurance medical fee payment. The unilateral cataract and bilateral cataract surgery fees were ¥121,000 and ¥242,000, respectively. We assumed that the cost of treating posterior capsule opacification (PCO) by neodymium:yttrium–aluminium-garnet (Nd:YAG) capsulotomy needed to be taken into account postoperatively for 11.4% of the patients according to the results of a meta-analysis of 6 prospective studies performed in Japan [19–24]. The other medical costs included the initial consultation, preoperative visit, cost of hospital treatment (postoperative medications, anesthesia fees, inpatient facility fee, eye examinations), and postoperative management (3 postoperative visits) associated with cataract surgery. The costs of complications other than PCO were not encompassed by the medical costs.

Cost-utility analysis was performed on the basis of the cost model and measured utility data. The utility gain was assumed to last until the end of the remaining statistical life expectancy of each patient as determined on the basis of the abridged life tables for 2008 in Japan [25]. The number of QALYs gained was calculated by multiplying the measured utility gain (difference in utility before and after surgery) and the patient's mean life expectancy, together with an assumed annual discount rate of 3%. The cost of cataract surgery was divided by the number of QALYs gained, which was estimated as Japanese yen/QALY (¥/QALY). The costs were converted into US dollars at a 2009 exchange rate of 93.68 Japanese yen to 1 US dollar (Federal Reserve; https://www.federalreserve.gov/releases/g5a/current/).

Statistical methods

Data were analyzed using Stata 10 software (StataCorp; College Station, TX). The results are given as the mean and standard deviation (SD), as the mean and 95% confidence interval (CI), or as the median. The significance of the difference in utility before and after cataract surgery was analyzed with a paired t test for dependent samples. An independent samples t test was used to compare the utility gain in unilateral surgery with that in bilateral surgery. Multiple linear regression models were used to assess the associated factors affecting utility at baseline for all patients. The regression model with robust standard errors (Eicker-Huber-White) was adjusted for age, sex, corrected distance visual acuity in the better-seeing eye (better VA), corrected distance visual acuity in the worse-seeing eye (worse VA), types of cataract, ocular past history, other ocular diseases, and the number of systemic comorbidities. First, each variable was analyzed in a univariate model. Then, all variables with a significance level (P) of less than 0.25 were included in a multivariate model. Because each of the clinical sites was an independent unit with its own examiners, infrastructure, and administrative structure for eye care, the assignment of patients was conducted separately and independently, and the cataract surgery procedures varied according to the clinical site. For analysis of the data pooled from the multiple centers, we also performed a meta-analysis to assess the utility gain after unilateral cataract surgery and bilateral cataract surgery. The random effect model was used to evaluate the pooled effect of the utility gain. Visual acuity data obtained by the decimal unit (counting fingers was categorized as an acuity of 0.004, hand motions as 0.002, and light perception as 0.001) were converted to logarithm of the minimal angle of resolution (LogMAR) units for statistical analysis. A P value of less than 0.05 was considered statistically significant.

Sensitivity analysis

One-way sensitivity analyses were performed by varying the discount rate of 0 and 5%, the cost by 25%, the cost excluding the PCO treatment cost, the treatment effectiveness using the results from the meta-analysis and within the 95% CI observed in the study, and survival in the short term (5 and 10 years).

Results

The age of the patients ($n = 549$) enrolled in the study ranged from 50 to 89 years (average, 71.0 ± 7.9 years; 214 men and 335 women). These 549 patients with complete data on visual acuity before surgery were available for inclusion in the study, and the utility from the TTO method ($n = 440$), EQ5D ($n = 541$) and HUI3 ($n = 496$) could be used in the analysis at baseline. Table 1 summarizes the characteristics of the samples at baseline. The baseline mean utility (TTO) (0.60) was lower than the utility of the EQ5D (0.84) and HUI3 (0.65).

The preoperative utilities (TTO) obtained from 440 patients at baseline were stratified according to the corrected distance visual acuity in the better VA (decimal) (Table 2). The utilities were correlated with 6 different visual stratifications. As the visual acuity in the better VA decreased, the corresponding utilities (TTO) decreased at every visual stratification level (Table 2).

Factors associated with preoperative utilities (TTO) are given in Table 3. In a multiple linear regression model adjusting for age, sex, visual acuity in the worse VA (logMAR), types of cataract, ocular history, ocular comorbidities, and the history of systemic comorbidities, the better VA (logMAR) showed a significant correlation with utilities (TTO). Utility changed by 0.21 for each change in visual acuity of one (logMAR) ($P < 0.001$; Table 3). Although age also had a significant effect, the regression coefficient was very small (−0.01), and the overall model was significant ($n = 429$, $F < 0.0001$, $R^2 = 0.10$).

Before the surgery, 15 patients cancelled undergoing cataract surgery, and by 3 months, 5 more patients had also withdrawn. Thus, complete data on visual acuity were obtained for 529 interventions. Although completed follow-up questionnaires were received from 490 patients, no method was provided to account for the missing values, and therefore, incomplete questionnaires were excluded. Finally, the utilities using the TTO method ($n = 381$), EQ5D ($n = 482$), and HUI3 ($n = 434$) could be used in the analysis of the final outcome.

Intraoperative techniques were phacoemulsification and aspiration with intraocular lens implantation in all cases. Out of 529 surgeries, 18 had the complication of posterior capsule rupture (3.4%). The mean better VA (logMAR) and worse VA (logMAR) improved to −0.05 ± 0.10 and 0.03 ± 0.25, respectively.

The study population consisted of 3 subgroups: group 1, in which both eyes were operated on ($n = 312$); group 2, in which only the first eye was operated on ($n = 157$); and group 3, in which the second eye was operated on (the first eye had been operated on previously) ($n = 60$). In the entire group of 381 participants, the overall utility (TTO) showed a statistically significant improvement from 0.60 at baseline to 0.85 3 months after cataract surgery. In the subgroup analysis, all groups showed a statistically significant improvement of utility in the TTO, EQ5D, and HUI3 (Table 4). The utility gain from the bilateral cataract operations was significantly higher than that from the unilateral cataract operations (combined first eye and second eye operations) in the TTO method ($P = 0.01$) and HUI3 ($P = 0.02$), but not in the EQ5D ($P = 0.88$). Tables 5 and 6 illustrate the combined effect of the pooled

Table 1 Patients' characteristics before surgery

Characteristic	n	Mean ± SD	Median
Age (years)	549	71 0 ± 7.9	71
Women	335	71.7 ± 7.5	72
Men	214	69.7 ± 8.4	70
VA (logMAR)	549		
Better eye		0.16 ± 0 28	0.1
Worse eye		0.51 ± 0.52	0.4
Utility			
TTO	440	0.60 ± 0 28	0.65
EQ5D	541	0.84 ± 0.15	0.79
HUI3	496	0.65 ± 0.24	0.69

VA visual acuity, *logMar* logarithm of minimal angle of resolution, *TTO* time tradeoff, *HUI3* Health Utility Index Mark 3

Table 2 Utility values associated with visual acuity in the better-seeing eye

Visual acuity (decimal)	Utility (TTO)	SD	n
<0.1	0.350	0.399	6
<0.2	0.419	0.289	8
<0.4	0.553	0.293	29
<0 8	0.558	0 293	167
<1 0	0.613	0.256	89
≥1 0	0.685	0 250	141
Overall	0.604	0.281	440

Table 3 Factors associated with preoperative utility

Variable	Univariate analysis			Multivariate analysis*		
	Coefficient	(95% CI)	*P* value	Coefficient	(95% CI)	*P* value
Age (per +1 year old)	−0.01	(−0.01 to −0.00)	<0.001	−0.01	(−0.01 to −0.00)	<0.01
Female (vs. male)	−0.06	(−0.12 to −0.01)	0.02	−0.05	(−0.10 to 0.01)	0.10
VA better (per +1 logMAR VA)	−0.25	(−0.34 to −0.15)	<0.001	−0.21	(−0.32 to −0.09)	<0.001
VA worse (per +1 logMAR VA)	−0.06	(−0.11 to −0.01)	0.02	0.00	(−0.05 to 0.06)	0.91
Nuclear cataract (present vs. absent)	0.00	(−0.07 to 0.06)	0.94			
Cortical cataract (present vs. absent)	−0.04	(−0.09 to 0.02)	0.20	−0.03	(−0.09 to 0.03)	0.32
PSC cataract (present vs. absent)	−0.04	(−0.10 to 0.01)	0.11	−0.05	(−0.11 to 0.01)	0.09
Ocular past history (present vs. absent)	0.01	(−0.07 to 0.09)	0.78			
Other ocular diseases (present vs. absent)	−0.05	(−0.13 to 0.03)	0.23	−0.03	(−0.11 to 0.05)	0.51
Systemic comorbidity[a]	−0.02	(−0.09 to 0.04)	0.48	0.00	(−0.06 to 0.06)	0.99
Systemic comorbidities[b]	−0.08	(−0.14 to −0.01)	0.03	−0.04	(−0.11 to 0.03)	0.25

VA better logMAR visual acuity in better-seeing eye, *VA worse* logMAR visual acuity in worse-seeing eye, *PSC* posterior subcapsular

*Only variables with a *P* value of less than 0.25 in the univariate analysis were included in the multivariate model

[a] One systemic comorbidity versus no systemic comorbidity

[b] More than 2 systemic comorbidities versus no systemic comorbidity

Table 4 Utility gain (before-and-after utility change by cataract surgery)

Characteristic	1st eye surgery	2nd eye surgery	Bilateral surgery
Age (mean ± SD)	69.0 ± 8.2	69.9 ± 7.9	72.2 ± 7.7
n	157	60	312
Utility (mean ± SD)			
TTO Utility (*n*)	109	38	234
Utility (before surgery)	0.66 ± 0.25	0.64 ± 0.29	0.58 ± 0.29
Utility (after surgery)	0.84 ± 0.28	0.88 ± 0.23	0.85 ± 0.25
Utility gain	0.18 ± 0.27	0.24 ± 0.30	0.27 ± 0.33
P value*	$P < 0.001$	$P < 0.001$	$P < 0.001$
EQ5D Utility (*n*)	138	52	292
Utility (before surgery)	0.85 ± 0.16	0.83 ± 0.16	0.84 ± 0.15
Utility (after surgery)	0.89 ± 0.15	0.92 ± 0.13	0.90 ± 0.15
Utility gain	0.05 ± 0.15	0.09 ± 0.17	0.06 ± 0.16
P value*	$P < 0.001$	$P < 0.001$	$P < 0.001$
HUI3 utility (*n*)	131	47	256
Utility (before surgery)	0.71 ± 0.25	0.70 ± 0.20	0.62 ± 0.24
Utility (after surgery)	0.79 ± 0.18	0.79 ± 0.22	0.76 ± 0.25
Utility gain	0.08 ± 0.21	0.08 ± 0.25	0.14 ± 0.25
P value*	$P < 0.001$	$P < 0.05$	$P < 0.001$

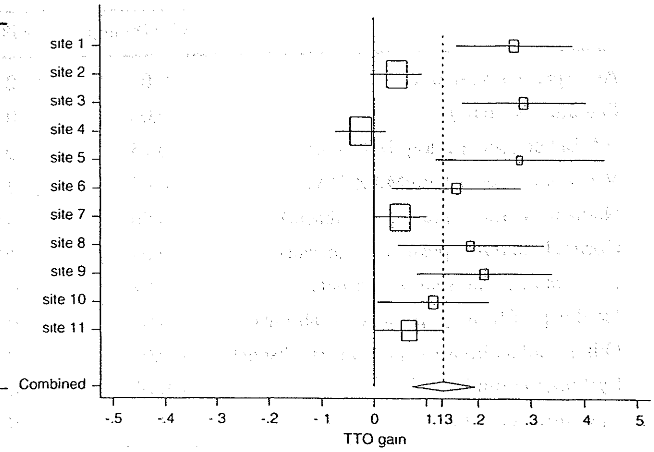
* The significance of the differences in utility before and after cataract surgery was analyzed with a paired *t* test

data of utility gain (TTO) obtained from the multiple centers The utility gain (TTO) was 0.13 for unilateral surgery and 0.26 for bilateral surgery when all clinical sites were combined in a meta-analysis using the random effect model.

Mean QALYs gained by cataract surgery, which were calculated by multiplying the utility gain [difference in utility (TTO) before and after surgery] and the life expectancy of each patient, together with an assumed annual discount rate of 3%, was 2.40 (95% CI 1.61–3.20) for unilateral operations (the first operation) and 3.40 (95% CI 2.86–3.95) for bilateral operations. The medical costs associated with unilateral cataract surgery and bilateral cataract surgery were estimated at ¥294,055 and ¥495,225, respectively (Table 7). This encompassed the hypothetical cost of YAG for 11.4% of the patients in the study. Given

Table 5 Meta-analysis utility gain (TTO) of unilateral surgery

Clinical sites	Weights	Utility gain	95% CI
Site 1	90.0	0.27	(0 16 to 0 38)
Site 2	116 8	0 04	(-0 01 to 0 09)
Site 3	86.9	0.29	(0 17 to 0 40)
Site 4	117.4	-0 03	(-0 07 to 0 02)
Site 5	68.5	0.28	(0.12 to 0 44)
Site 6	83 6	0 16	(0.03 to 0.28)
Site 7	116.2	0 05	(-0 00 to 0 10)
Site 8	76.6	0 19	(0.04 to 0 33)
Site 9	81 8	0.21	(0.08 to 0.34)
Site 10	91 8	0 11	(0 01 to 0 22)
Site 11	111 0	0.07	(0 00 to 0.13)
Combined		0 13	(0 07 to 0 19)



the cost of cataract surgery, the resultant cost-effectivenesses (¥/QALY) gained from unilateral cataract surgery and bilateral cataract surgery were found to be ¥122,472/QALY and ¥145,526/QALY, respectively. Based on the 2009 yen-US dollar exchange rate, $/QALYs gained from unilateral cataract surgery and bilateral cataract surgery were calculated to be $1,307/QALY and $1,553/QALY, respectively. The results from the utility gains in the EQ5D and HUI3 are also given in Table 8.

Sensitivity analysis

In one-way sensitivity analysis, the cost per QALY was relatively robust against discounting or varying the cost (Table 9). Our results did not vary significantly when varying the treatment effectiveness according to the results of the meta-analysis and were within the range of 95% CI observed in the study. However, varying the life expectancy resulted in a substantially increased cost per QALY.

Discussion

Cost-utility analysis is a type of economic evaluation that quantifies the cost-effectiveness of a process, such as a treatment, a screening, or a diagnostic examination, through the measurement of QALYs in which years of life are adjusted using utility as qualitative weighted factors. Cost-utility analysis is increasingly advocated as a method for assessing the value for money of different health-care interventions since it allows for a comparison of health-care interventions across all medical specialties. Previous studies have demonstrated that cataract surgery is a very cost-effective procedure in medicine [8, 11, 26, 27], and the results of our analysis provide support that this is also the case in Japan. The data presented herein show that cataract surgery yields a ¥/QALY gain of ¥122,472 ($1,307) for unilateral surgery and ¥145,526 ($1,553) for bilateral surgery using TTO utility, a 3% discount rate, and nominal 2009 US dollar-yen exchange rate. The results of our study were roughly comparable to those reported by Busbee ($2,020, first eye; $2,727, second eye) [8, 27]. While there is no explicit threshold for the incremental cost per QALY, there is some consensus on the rule of thumb that costs are economically attractive below $20,000 per QALY, are acceptable up to $50,000 per QALY, and are possibly acceptable up to $100,000 per QALY [28, 29]. Therefore, considering cost, our study has demonstrated that cataract surgery is extremely cost-effective not only for one eye, but also for both eyes. Most previous studies demonstrated the cost-utility of cataract surgery only for one eye. However, because approximately 60% of the patients in our study had cataract surgery in both eyes, our result indicates that the cost-utility of bilateral cataract surgery is virtually identical to that of "incremental" cataract surgery in the actual situation in Japan.

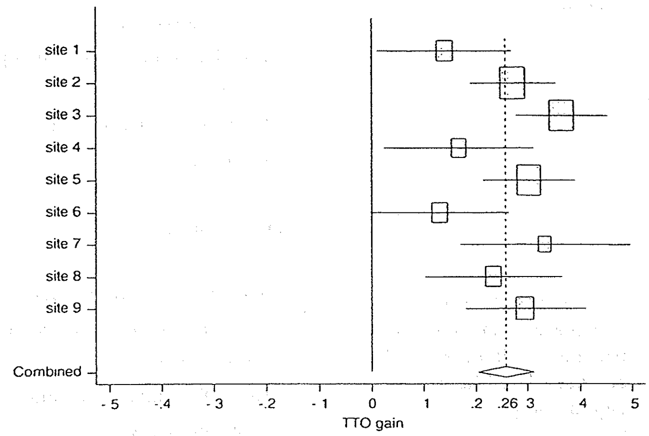
Many of the previous reports were based on models or registry data rather than on a real-world setting [8, 9], indicating that previous estimates were based on observed visual acuity data translated into utility, not on actual measurement of utility obtained from individual patients, as in our study. We measured each patient's utility before and after surgery at 3 months; thus, the change in the utility can reflect the direct effect of utility gained by the cataract surgery without the involvement of other comorbidities.

Although several methods are available to measure utility, the TTO method requires patients to decide which health state they prefer—their present health state or a normal health state in return for which they give up time of life—and thus, it can directly measure the preference-based QOL of patients. Time tradeoff utility is reproducible and reliable on a test-retest basis over a prolonged period of

Table 6 Meta-analysis: utility gain (TTO) of bilateral surgery

Clinical sites*	Weights	Utility gain	95%CI
Site 1	130.3	0.14	(0.01 to 0.27)
Site 2	196 8	0.27	(0.19 to 0.36)
Site 3	188.7	0.37	(0.28 to 0 45)
Site 4	114.2	0.17	(0.02 to 0.31)
Site 5	187 2	0.30	(0.21 to 0.39)
Site 6	125.6	0.13	(-0.00 to 0.26)
Site 7	97.2	0.33	(0.17 to 0 50)
Site 8	127.7	0 23	(0.10 to 0 37)
Site 9	149 0	0.30	(0 18 to 0.41)
Combined		0 26	(0.20 to 0 31)

* Owing to the small sample size, 2 sites were excluded from the analysis



time and has excellent intraobserver and interobserver reliability [14, 30]. At the same time, it is applicable to all health states and readily understood by patients, and thus regarded as the most suitable instrument for use in cost-utility analysis [14]. Therefore, the TTO method is accepted as a formal method for quantifying the relative impact of a given health state or disease on patient lives [8, 14, 26, 31, 32]. To measure the utility gain from ophthalmic treatment, the TTO method is more sensitive to small changes in utility than are generic survey questionnaires, such as the EQ5D and HUI3. The EQ5D does not address visual impairment, and the HUI3 has only 2 questions about sight out of 16 questions. Predictably, the utility measured by the TTO method showed higher improvement than did those of the EQ5D and HUI3 in our study. While using generic measures should theoretically allow us to compare results for a variety of different health states, as revealed by previous studies [33–37], our study has shown that disparities exist in the utilities derived from the EQ5D and HUI3.

Utility associated with ophthalmic disease has been most highly correlated with better VA [38]. Data from the analysis presented here also indicate the same relation between visual acuity and utility Vision is only one of the many factors affecting utility; thus, the vision improvement resulting from cataract surgery seemed to account for a small part of the change in utility. However, the effect of cataract surgery on utility (TTO) was highly significant. Moreover, our findings indicated that even in the utility gain demonstrated by the EQ5D and HUI3, the change in utility was significant. In our study, 144 of 440 patients had better VA of >1 0 (decimal), and the corresponding utilities (TTO) were fairly low (0 685) However, even in the patients with better VA of >1 0 (decimal), a mean utility gain of 0.18 was obtained by cataract surgery. This means that while for clinicians visual acuity is the precise and most important standard to measure the effectiveness of the surgery, it is not so for patients. Although visual acuity is the most important predictive factor of utility, patients place emphasis on their daily life activities and overall subjective quality of life.

One of the most outstanding features of cataract surgery is its ease of maintenance of the visual outcome After a few months for recovery from the surgery, patients usually do not need any medication or additional treatment for the rest of their lives, and therefore, the additional medical costs are very low. Another feature is the long duration of the benefit of visual outcome. Posterior capsule opacification is the most common long-term complication after cataract surgery, with an estimated incidence of almost 11.4% [19–24], but usually visual losses due to PCO are not very severe. Even for cases of PCO, a one-time YAG capsulotomy can provide lifelong recovery of good vision. Lundstrom and Wendel's long-term study showed that 80% of the patients who had cataract surgery still had improved visual function 7 years after surgery [39]; therefore, the cost-utility of cataract surgery is valid for the life span of the patient.

Some limitations in this study must be considered. Although the common inclusion and exclusion criteria for selection of the patients were established, the study population was not randomly selected at each clinical site. In addition, owing to incomplete questionnaires and withdrawal of patients from the study, complete data for utility (TTO, EQ5D, and HUI3) were obtained from 381, 482, and 434 patients, respectively Despite this potential source of error in the outcome measures, our samples were not random but representative of the current situation of cataract surgery in Japan since they were large samples obtained

Table 7 Medical costs (2009 nominal Japanese yen-US dollar exchange rate)

Services	Costs (yen)	(US $)[b]
Cataract surgery (1 eye)		
Initial consultation and preoperative visit	¥27,070	US$289
Surgical fee	¥121,000	US$1,292
Cost of hospital treatment	¥127,680	US$1,363
Postoperative visit	¥15,250	US$163
	Subtotal ¥291,000	US$3,106
PCO treatment (1 eye)	¥26,800	US$286
	Total ¥294,055[a]	US$3,139
Cataract surgery (both eyes)		
Initial consultation and preoperative visit	¥27,070	US$289
Surgical fee	¥242,000	US$2,583
Cost of hospital treatment	¥201,260	US$2,148
Postoperative visit	¥19,980	US$213
	Subtotal ¥490,310	US$5,234
PCO treatment (both eyes)	¥43,120	US$460
	Total ¥ 495,225[a]	US$5,286

[a] Value based on the assumption that 11.4% of the patients would develop PCO and need YAG laser capsulotomy

[b] Costs were converted into US dollars using the 2009 foreign exchange rate of 1 US $ = 93.68 Japanese yen (Federal Reserve)

Table 8 Cost-utility of cataract surgery

Group	QALYs gain	Cost	Cost/QALY (yen)	(US dollars)
One eye[a]				
TTO	2 40	¥294,055	¥122,472	US$1,307
EQ5D	0 81		¥364,380	US$3,890
HUI3	1 36		¥216,058	US$2,306
Both eyes				
TTO	3 40	¥495,225	¥145,526	US$1,553
EQ5D	0 75		¥659,421	US$7,039
HUI3	1 85		¥267,834	US$2,859

[a] The utility gain in 1 eye used here is the utility gain for the first eye operation

Table 9 Cost-utility sensitivity analysis

	One eye			Both eyes		
	TTO	EQ5D	HUI3	TTO	EQ5D	HUI3
Base case	¥122,472	¥364,380	¥216,058	¥145,526	¥659,421	¥267,834
Varying the discount rate (%)						
0	¥94,582	¥267,080	¥159,639	¥115,115	¥527,396	¥208,780
5	¥142,193	¥436,283	¥257,266	¥166,742	¥751,480	¥309,322
Varying treatment effectiveness						
Meta-analysis utility[a]	¥168,590	¥487,446	¥287,468	¥146,365	¥629,371	¥246,812
QALYs (upper 95% CI)	¥92,036	¥245,046	¥154,198	¥74,539	¥297,025	¥130,286
QALYs (lower 95% CI)	¥182,984	¥701,802	¥360,362	¥102,780	¥573,207	¥204,063
Varying life expectancy (years)						
5	¥354,710	¥1,284,083	¥738,832	¥387,197	¥1,725,523	¥745,821
10	¥190,450	¥688,653	¥396,835	¥207,903	¥925,654	¥400,020
Varying costs						
Increased by 25%	¥153,090	¥455,476	¥270,073	¥181,908	¥824,276	¥334,792
Decreased by 25%	¥91,854	¥273,285	¥162,044	¥109,145	¥494,566	¥200,875
Without PCO treatment	¥121,200	¥360,595	¥213,813	¥144,082	¥652,876	¥265,176

[a] The utility gain from the results of the meta-analysis and the mean life expectancy of the whole sample (16 3 years) were used

from 12 different clinical sites that included university hospitals, general hospitals, and private practices. The mean age and postoperative better VA of the missing samples did not significantly differ from the values of the entire sample, indicating that there was no difference between patients who answered all the questions on the follow-up questionnaire and those who did not. Another limitation of this study was the incomplete analysis of all the incremental costs of cataract surgery or of those induced by performing surgery versus no surgery. In this study, only the direct cost (including PCO treatment for 11.4% of the patients) without any complications was assessed. An in-depth cost analysis, the influence of complications, and a risk analysis may provide further understanding of the cost-effectiveness of cataract surgery.

In summary, routine cataract surgery in Japan is highly cost-effective, not just for unilateral surgery, but also for bilateral surgery. Contributing factors are the high clinical effectiveness of the surgery, the substantial improvement in patient-perceived quality of life, and the reasonable cost of the surgery. These results were strongly supported by the results derived from the generic outcome measures, such as the EQ5D and HUI3, and this consistency supports the validity and generalizability of our findings. Given the limited resources for health care, cataract surgery is one of the most powerful health-care interventions to produce great health gains for a great number of people at low cost This information, taking into account the clinical effectiveness that incorporates patient preferences and cost, will play an increasingly crucial role in the evaluation of health care in the future.

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Appendix

The Eye Care Comparative Effectiveness Research Team (ECCERT)

The following individuals participated in this study

Corresponding author: Yoshimune Hiratsuka

Writing Committee: Yoshimune Hiratsuka, Masakazu Yamada, Akira Murakami, Annabelle Ayame Okada, Hidetoshi Yamashita, Yuichi Ohashi, Naoya Yamagishi, Hiroshi Tamura, Shunichi Fukuhara, and Tomoyuki Takura

The Study Group Investigators and the Clinical Sites
Eguchi Ganka Hospital, Hokkaido Shuichiro Eguchi.
Iwate Medical University, Iwate Daijiro Kurosaka
Yamagata University, Yamagata Hidetoshi Yamashita
National Hospital Organization Tokyo Medical Center, Tokyo: Masakazu Yamada.
Kyorin Eye Center, Tokyo: Annabelle Ayame Okada.
Juntendo University School of Medicine, Tokyo: Akira Murakami, Koichi Ono.
Juntendo Tokyo Koto Geriatric Medical Center, Tokyo: Yoshimune Hiratsuka, Kenichi Takahashi.
Shohzankai Medical Foundation Miyake Eye Hospital, Nagoya: Sampei Miyake.
National Hospital Organization Nagoya Medical Center, Nagoya: Hiroshi Hirose.
National Hospital Organization Osaka Medical Center, Osaka: Yasumasa Otori.
Kyoto University, Kyoto: Nagahisa Yoshimura, Hiroshi Tamura.
Ehime University, Ehime: Yuichi Ohashi, Toshihiko Uno, Yasuaki Yamamoto.

Central Unit: National Institute of Sensory Organs, National Hospital Organization Tokyo Medical Center, Tokyo: Masakazu Yamada.

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CLINICAL INVESTIGATION

Quality of life and cost-utility assessment after strabismus surgery in adults

Keiko Fujiike · Yoshinobu Mizuno · Yoshimune Hiratsuka · Masakazu Yamada · The Strabismus Surgery Study Group

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Abstract

Purpose To understand the functional and psychosocial aspects of strabismus surgery, an evaluation based on the patient's perspective is essential. In this study, we assessed quality of life and utility in adult patients who had undergone strabismus surgery, and we modeled the cost of providing this intervention in order to calculate the cost-utility of strabismus surgery in adults.

Methods The study population comprised 226 patients with strabismus aged 18 years or older who were scheduled for ocular alignment surgery at 12 facilities of the Strabismus Surgery Study Group in Japan. Survey questionnaires consisting of the Japanese versions of the Visual Function Questionnaire-25 (VFQ-25) and 8-Item Short-Form Health Survey (SF-8) and utility assessment by a time trade-off method were administrated preoperatively and 3 months postoperatively. On the basis of the cost model and measured utility data, the gains in quality-adjusted life years (QALYs) and $/QALY were estimated.

Results Postoperatively, the subscale scores of the VFQ-25 and the physical and mental component summary scores of the SF-8 showed a statistically significant improvement. A significant improvement of utility was also noted: 0.82 ± 0.28 postoperatively versus 0.76 ± 0.31 preoperatively. On the basis of the life expectancy of these patients and the cost model, the surgery resulted in a mean value gain of 0.99 QALYs and a cost-utility for strabismus surgery of 1,303 $/QALY.

Conclusions By using standard tools to assess vision-associated and general health status, we confirmed the psychosocial benefits of corrective surgery for adults with strabismus. Our study concurrently demonstrated that strabismus surgery in adults is very cost-effective.

Keywords Burden of disease · Quality of life · Strabismus · Utility · VFQ-25

K. Fujiike · Y. Mizuno · M. Yamada (✉)
Division for Vision Research, National Institute of Sensory Organs, National Tokyo Medical Center, 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-8902, Japan
e-mail. yamadamasakazu@kankakuki.go.jp

Y. Hiratsuka
Department of Management Science, National Institute of Public Health, Wako, Japan

Introduction

Several studies have demonstrated favorable clinical and functional outcomes of strabismus surgery in adults [1–6]. Elimination of diplopia, sensory fusion, restoration of binocularity, and expansion of the binocular visual fields are recognized as functional outcomes of adult strabismus surgery. An additional aspect of adult strabismus is psychosocial functioning [1, 7–9]. Olitsky and associates [8] reported that strabismic participants were more likely to be perceived as being less intelligent and less competent and as having poorer communication skills than orthotropic participants. Coats and associates [9] reported potential adverse vocational implications of strabismus. These negative social impacts associated with noticeable strabismus are likely to cause patients to develop psychological difficulties. Menon and associates [10] reported that 80% of patients with strabismus felt that they had problems in their social lives and that a positive change in self-esteem and self-confidence was noticed by 95% of the patients after surgery. Satterfield and associates [11] reported that correction of strabismus in adults might offer improvement in psychosocial functioning. From these observations, a recent report of the

American Academy of Ophthalmology concluded that surgical treatment of strabismus in adults is generally safe and effective in improving ocular alignment [12].

Despite these favorable outcomes, the value of adult strabismus surgery appears to be underestimated and is sometimes regarded as only a cosmetic treatment, even by ophthalmologists [13]. Unlike other eye surgeries, such as cataract surgery and retinal detachment surgery, adult strabismus surgery does not usually improve the visual acuity nor save the eyes from permanent visual loss. To capture the multidimensional outcomes of strabismus surgery including the functional and psychosocial aspects, evaluation based on the patient's perspective is important. For patient-based outcomes, quality of life (QOL) assessment and utility analysis are generally used. In the field of ophthalmology, assessment of the impact of eye disease on the daily lives of patients and on social economics has been actively performed in the United States and European countries [14–17]. Regarding strabismus surgeries, however, there are as yet few reports that use quantitative measurement to evaluate the functional and psychosocial benefits and also assess the cost-utility of strabismus surgery [18, 19].

For quantitative evaluation of QOL, it is essential to apply measurement tools with verified reliability and validity. Hence, the Japanese versions of the Visual Function Questionnaire-25 (VFQ-25) and 8-Item Short-Form Health Survey (SF-8) were selected for this study [20, 21]. The VFQ-25, originally developed by Mangione and associates [22], has become the standard tool to assess vision-related QOL. The SF-8 is a shortened form of the standard tool for generic QOL, the 36-Item Short-Form Health Survey (SF-36) [23].

Another method adopted in the present study was utility assessment, which summarizes QOL status as a single number [24]. Utility assessment is a formal method for quantifying the relative impact of a given health state or disease on a patient's life. Although several methods have been developed to assess utility, the time trade-off method is the most standard and widely used [24, 25]; hence, it was used in this study. Utilities could be used to compare patients' preferences for strabismus outcomes with those for different symptomatic medical conditions, such as angina, asthma, and visual impairment [26–28]. They could also be used as weights in the calculation of quality-adjusted life years (QALYs), which are used as denominators in cost-utility analyses [26–28]. The outcome of an intervention is thus evaluated by offsetting the cost of the intervention with QALYs gained from the intervention. In this study, we assessed the utilities in adult patients who underwent strabismus surgery and modeled the cost to provide this intervention in order to calculate the cost-utility of strabismus surgery in adults.

Participants and methods

This multicenter study was conducted at 12 facilities of the Strabismus Surgery Study Group in Japan (see Appendix). The inclusion criteria were that the patients had to be aged 18 years or older and scheduled for strabismus surgery at any of these facilities. Patients who were unable to answer the survey questionnaire or who planned to undergo surgery or laser treatment for an ocular comorbidity were excluded. The principles of the World Medical Association Declaration of Helsinki were followed. Each patient received a thorough explanation of the purpose of the study and of all the procedures involved in the study and had the opportunity to examine the informed consent form prior to enrollment. The protocol was approved by the institutional review board of each facility, and all patients provided written informed consent.

Registration of the patients was carried out between March 2007 and November 2008 with 273 patients being initially registered. Later, however, owing to reasons including withdrawal of consent, insufficient information on clinical findings from the responsible physicians, and inability to collect survey forms from patients, we were unable to obtain complete information on 47 patients. Therefore, the final number of participants was 226 after exclusions.

For the 226 registered patients, information on ophthalmological findings was collected from the responsible physicians, and information on QOL and utility assessment collected from the patients by means of survey questionnaires. The questionnaires consisted of the Japanese versions of the VFQ-25 and SF-8 and of a questionnaire for the time trade-off measurements. The reliability and validity of the Japanese versions of the VFQ-25 and SF-8 are considered comparable to the English versions [20, 21].

Utility is defined on a continuous scale from 0 to 1, where 0 corresponds to the worst possible QOL weight (equal to death) and 1 to the best possible QOL weight (equal to perfect health). The time trade-off method used in the study consisted of 2 questions [19, 24]. In the first question, the patient was asked to estimate his/her own life expectancy. The patient was then asked if he/she would be willing to trade a certain portion of the remaining life from the estimated life expectancy (off the end of his/her life) in return for being free from strabismus and all its associated effects under these hypothetical conditions. Time trade-off utility was calculated according to the following equation: Utility $= 1 - x/t$ (where $x =$ years of life he/she would be willing to give up and $t =$ his/her own life expectancy). After having had the questionnaires explained to them, the patients were asked to fill them out at home and to return them by post. The surveys were distributed preoperatively, either at the initial consultation or at the preoperative visit, and 3 months postoperatively.

All medical costs in Japan are uniformly standardized by a social medical insurance system. Medical costs associated with strabismus surgery were calculated on the basis of the Japanese Social Insurance Medical Fee Payment for fiscal year 2008 (Table 1). The surgical fee was calculated from the information regarding the number and type of surgery performed for each case. Other medical costs included the initial consultation, preoperative visit, anesthesia fees, postoperative medication, and 3 postoperative visits (the next day, 1 week, and 1 month after surgery). For cases in which a second operation was performed because the first operation was not adequate, an additional surgical fee, postoperative drug costs, and costs for 3 postoperative visits were added. The costs of complications were not included in the medical cost model.

Cost-utility analysis was performed on the basis of the cost model and measured utility data. The utility gain was assumed to last until the end of the remaining life expectancy of each patient as estimated using the abridged life tables for 2008 in Japan. The number of QALYs gained was calculated by multiplying the measured utility gain (difference in utility before and after surgery) and the patient's life expectancy, together with an assumed annual discount rate of 3%. The cost for strabismus surgery was divided by the number of QALYs gained, which resulted in an estimate of Japanese yen/QALY. The $/QALY was calculated on the basis of the yen–US dollar exchange rate in November 2008 (1 US dollar = 96.4 Japanese yen). One-way sensitivity analyses were performed by varying the discount rate of 0 and 5%, medical cost of 25%, utility gain within the 95% confidence interval (CI) observed in the study, and duration of alignment in the shorter term (5, 10, and 20 years).

For statistical analyses, IBM SPSS Statistics software (IBM SPSS Japan, Tokyo, Japan) was used. The results were given as the mean and standard deviation (SD) or as the mean and 95% CI. The significance of the differences was analyzed with the Wilcoxon signed rank test or the chi-squared test. A probability value <0.05 was considered statistically significant. Multiple linear regression models were used to assess the associated factors affecting postoperative utility value. The regression model was adjusted for age, sex, type of strabismus, cure grades based on the Japanese criteria, postoperative composite VFQ-25 score, and summary SF-8 scores. Each variable was first analyzed in a univariate model and then all variables were included in a multivariate model.

Table 1 Medical costs associated with extraocular muscle surgery for strabismus in Japan

Service	Cost (yen)
Initial consultation and preoperative visit	21,000
Surgical fee	
Recession	42,800
Resection	42,000
Recession and resection	84,400
Oblique muscle surgery	66,100
Horizontal and oblique muscle surgery	94,300
Muscle transposition	124,000
Anesthesia fee and postoperative drug costs	6,000
Three postoperative visits	10,000

Results

The 226 patients (106 men and 120 women) enrolled in the study ranged in age from 18 to 87 years (average 45.7 ± 18.5 years) (Table 2). Of these, 168 patients were diagnosed as having concomitant strabismus (CS group; 136 patients with exotropia and 32 with esotropia) and 58 patients with noncomitant strabismus (NCS group; 38 patients with paralytic strabismus, 17 with restrictive strabismus, and 3 with strabismus of unknown etiology). When the patients were divided into the CS group or NCS group, there were no statistical differences in age and sex between the 2 groups. Approximately one half of the patients in the CS group had congenital or childhood-onset strabismus ($P < 0.001$, chi-squared test), and 32 cases (19.5%) had a history of previous strabismus surgery ($P < 0.01$, chi-squared test). In contrast, 70.7% of patients in the NCS group were adulthood-onset patients and likely to suffer from diplopia ($P < 0.001$, chi-squared test).

There were no major surgical complications such as postoperative infections, lost muscles, and refractory diplopia (Table 3); however, 16 patients (8 in the CS group and 8 in the NCS group) required additional surgery because of inadequate alignment. When postoperative conditions were classified according to the Japanese criteria of strabismus cure [29], 38 patients (16.8%) were classified as excellent, 41 (18.1%) as good, 5 (2.2%) as fair, 100 (44.2%) as cosmetically satisfactory, and 42 patients (18.6%) as not improved. Difference in the grades of cure status between the CS and NCS groups was not statistically significant (Pearson's chi-squared test).

The VFQ-25 scores of the participants are shown in Table 4. The VFQ-25 scores are expressed from 0 to 100 by each subscale with 0 representing the worst and 100 the best. One hundred and fifty participants (68.1%) answered the driving subscale of the questionnaire; the remaining participants who did not drive completed the rest of the questionnaire. When the postoperative subscale scores of the VFQ-25 were compared with those obtained

Table 2 Demographic features of study participants preoperatively

	Strabismus patients enrolled in the study		
	CS ($n = 168$) (%)	NCS ($n = 58$) (%)	Total ($n = 226$) (%)
Age (mean ± SD, years)	45.1 ± 18.4	47.6 ± 18.7	45.7 ± 18.5
Sex			
Male	82 (48.8)	24 (41.4)	106 (46.9)
Female	86 (51.2)	34 (58.6)	120 (53.1)
Onset of strabismus			
From birth/childhood	88 (52.4)	17 (29.3)	105 (46.4)
Adulthood	69 (41.1)	41 (70.7)	110 (48.7)
Unknown	11 (6.5)	0	11 (4.9)
Direction of strabismus			
Esotropic	32 (19.0)	13 (22.4)	45 (19.9)
Exotropic	136 (81.0)	1 (1.7)	137 (60.6)
Vertical	0	28 (48.3)	28 (12.4)
Others	0	16 (27.6)	16 (7.1)
Previous strabismus surgery	32 (19.5)	2 (3.4)	34 (15.0)
Presence of diplopia	35 (20.8)	41 (70.7)	76 (9.5)

CS concomitant strabismus, *NCS* noncomitant strabismus

Table 3 Surgical results of study participants

	Strabismus patients enrolled in the study		
	CS ($n = 168$) (%)	NCS ($n = 58$) (%)	Total ($n = 226$) (%)
Major complications	0 (0.0)	0 (0.0)	0 (0.0)
Additional surgery	8 (4.8)	8 (13.8)	16 (7.1)
Cure status			
Grade 4: excellent	26 (15.5)	12 (20.7)	38 (16.8)
Grade 3: good	28 (16.7)	13 (22.4)	41 (18.1)
Grade 2. fair	5 (3.0)	0 (0.0)	5 (2.2)
Grade 1: cosmetically satisfactory	76 (45.2)	24 (41.3)	100 (44.2)
Grade 0: not improved	33 (19.6)	9 (15.5)	42 (18.6)

CS concomitant strabismus, *NCS* noncomitant strabismus

preoperatively, all VFQ-25 subscales except for the general health subscale in the NCS group showed a statistically significant improvement ($P < .05$, Wilcoxon signed rank test).

The SF-8 scores of the participants are shown in Table 5. The SF-8 scores including the physical and mental component summary scores were all between 45 and 50. When the preoperative and postoperative subscale SF-8 scores of all participants were compared, 6 out of 8 subscales (not the bodily pain and vitality subscales) showed statistically significant differences ($P < 0.05$, Wilcoxon signed rank test). The differences between the summary scores for the physical and mental component scores were statistically significant ($P < 0.05$, Wilcoxon signed rank test).

The distribution of utility is shown in Fig. 1. Thirty-three patients were excluded because they did not answer the questions that determine utility values. The profile of these 33 patients did not significantly differ in age, sex, and types of strabismus from those of the remaining 193 patients. Of the 193 patients who completed the time trade-off questionnaire, 39 indicated the same utility before and after surgery, 4 reported a loss in utility, and the remaining 150 patients reported a gain in utility. Overall, the mean utility value in the preoperative period was 0.76 ± 0.31 (Table 6). Postoperatively, the mean utility value was 0.82 ± 0.28, resulting in a 0.05 ± 0.15 gain in utility. Statistical differences in preoperative utility, postoperative utility, and gain in utility were not observed between the CS and NCS groups (Wilcoxon signed rank test).

Factors associated with postoperative utility are shown in Table 7. When each variable was analyzed in a univariate model, postoperative utility had a significant, but weak correlation with age, VFQ-25 composite score, and SF-8 physical component summary score ($r = -0.303$, $r = 0.187$, and $r = 0.252$, respectively; Pearson's product-

Table 4 Preoperative and postoperative VFQ-25 subscale scores of the participants

Subscales	CS ($n = 168$)		NCS ($n = 58$)		Total ($n = 226$)	
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
General health	60.8 ± 18.1	65.1 ± 18.5*	55.9 ± 18.7	59.2 ± 17.5	59.5 ± 18.3	63.3 ± 18.8*
General vision	58.8 ± 19.1	73.2 ± 15.9*	50.8 ± 19.3	69.8 ± 16.6*	56.7 ± 19.4	72.4 ± 16.0*
Ocular pain	76.0 ± 20.4	82.3 ± 15.6*	69.0 ± 24.8	79.5 ± 19.1*	74.2 ± 21.8	81.5 ± 16.5*
Near vision	75.0 ± 18.0	83.8 ± 14.7*	68.2 ± 19.1	77.6 ± 17.1*	73.2 ± 18.5	82.3 ± 15.3*
Distance vision	72.3 ± 18.9	82.7 ± 14.8*	65.5 ± 21.1	76.9 ± 16.1*	70.5 ± 19.7	81.3 ± 15.1*
Vision-specific						
Social functioning	82.0 ± 16.3	89.8 ± 13.0*	75.8 ± 21.1	85.6 ± 12.6*	80.4 ± 17.9	88.9 ± 12.8*
Mental health	65.2 ± 23.7	79.9 ± 18.3*	52.1 ± 25.8	72.3 ± 24.2*	61.8 ± 24.9	78.1 ± 20.2*
Role difficulties	81.2 ± 18.5	88.4 ± 15.4*	69.2 ± 21.8	80.0 ± 19.2*	78.1 ± 20 0	86.3 ± 16 8*
Dependency	85.4 ± 19.3	91.6 ± 14.5*	79.7 ± 23.7	87.0 ± 19.3*	83.9 ± 20.6	90.4 ± 15.9*
Driving	71.6 ± 26.4	77.5 ± 22.3*	58.1 ± 31.7	72.4 ± 26.8*	68.1 ± 28.4	75.9 ± 23.9*
Color vision	91.0 ± 13.8	93.3 ± 12.1*	86.2 ± 15.8	91.7 ± 11.9*	89.8 ± 14.5	93.0 ± 12.0*
Peripheral vision	64.8 ± 23.2	75.2 ± 21.4*	57.6 ± 29.7	68.0 ± 24.4*	63.0 ± 25.2	73.6 ± 22.2*
Composite score	73.5 ± 15.2	81.9 ± 12.0*	65.9 ± 18.3	76.7 ± 13.8*	71.6 ± 16 3	80.6 ± 12.6*

Results are expressed as mean ± SD

CS concomitant strabismus, *NCS* noncomitant strabismus

* Statistically significant difference ($P < 0.05$, Wilcoxon signed rank test)

Table 5 Preoperative and postoperative SF-8 subscale scores of the participants

Subscales	CS ($n = 168$)		NCS ($n = 58$)		Total ($n = 226$)	
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
General health	49.9 ± 6.8	51.8 ± 6.3*	49.1 ± 7.1	50.3 ± 7.1	49.7 ± 6.9	51.4 ± 6.6*
Physical functioning	47.9 ± 6.0	49.6 ± 6.7	47.4 ± 6.4	48 9 ± 5.9*	48.6 ± 6.2	49.4 ± 6.5*
Role physical	47.5 ± 7.6	49.9 ± 6.0	44.8 ± 11 3	48.5 ± 6.9*	47.7 ± 8.8	49.5 ± 6.3*
Bodily pain	52.0 ± 8.5	52.5 ± 8.8	51.3 ± 9 2	53.6 ± 8.8*	52.2 ± 8.7	52.8 ± 8.8
Vitality	50.6 ± 6.2	51.3 ± 6.6	49.9 ± 7.3	51.1 ± 6.4	50.6 ± 6.5	51.3 ± 6.5
Social functioning	46.7 ± 8.5	49.3 ± 7.8*	46.5 ± 9.6	47.4 ± 8.4	47.2 ± 8.8	48.8 ± 8.0*
Mental health	49.1 ± 7.1	50 3 ± 7.3*	46.0 ± 6.9	48.9 ± 7.4*	48.2 ± 7.1	49.9 ± 7.3*
Role emotional	47.7 ± 7.0	49.9 ± 6.4*	45.6 ± 10 4	48.7 ± 5.8*	47.7 ± 8.0	49.6 ± 6.3*
Physical component summary	48.6 ± 7.0	50.0 ± 6.6	47.7 ± 7.8	49.5 ± 7.4*	49.1 ± 7.3	49.8 ± 6.8*
Mental component summary	47.7 ± 7.2	49.2 ± 7.0*	45.3 ± 7.9	47.3 ± 8.0	47.0 ± 7.4	48.7 ± 7.3*

Results are expressed as mean ± SD

CS concomitant strabismus, *NCS* noncomitant strabismus

* Statistically significant difference ($P < 0.05$, Wilcoxon signed rank test)

moment correlation). In a multiple linear regression model adjusting for age, sex, type of strabismus, postoperative cure grade, VFQ-25 composite score, and SF-8 physical and mental component summary scores, only age had a significant effect, although the standardized β coefficient was small (−0.004).

The QALYs gained by the surgery, which were calculated by multiplying the utility gain (difference in utility before and after surgery) and the patient's life expectancy, together with an assumed annual discount rate of 3%, was 0.99 ± 2.89. The average medical cost associated with extraocular muscle surgery for strabismus was 124,926 ± 32,395 yen. Given the cost of strabismus surgery, this resulted in a cost-utility of 125,630 ± 41,728 yen/QALY. The $/QALY, calculated based on the yen–US dollar exchange rate in November 2008, was 1,303 ± 434 $/QALY. Differences in QALYs gained by surgery, medical costs, and yen/QALY ($/QALY) between the CS and NCS groups were not statistically significant (Wilcoxon signed rank test).

In the one-way sensitivity analysis, the cost per QALY was relatively robust against the varying discount rate or varying cost (Table 8). Our results did not differ significantly when varying the utility gain within the range of 95% CI observed in the study. Varying the duration of alignment, however, resulted in substantially increased cost per QALY.

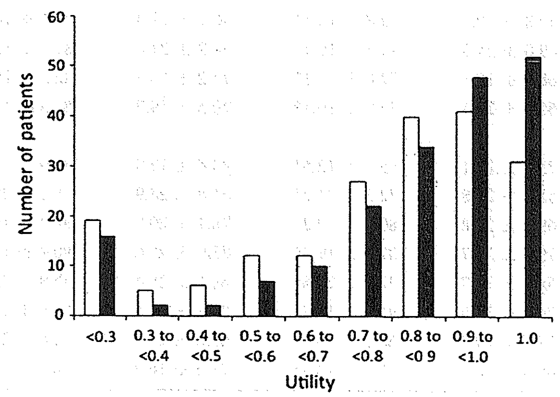

Fig. 1 Distribution of preoperative (*white bars*) and postoperative (*black bars*) utilities as measured by the time trade-off method

Discussion

To capture a person's health status is not simple, considering the multidimensional and multifactorial natures of QOL [22–24]. Nevertheless, numerous methods have recently been developed to measure QOL status, mainly because the importance of evaluation based on the patient's perspective has become widely recognized. In the current study, we used 2 different measures: QOL assessment through survey questionnaires and utility analysis to quantitatively evaluate the effect of adult strabismus surgery on patients' QOL.

This study used the VFQ-25 and SF-8 as QOL questionnaires for over 200 surgical cases of strabismus in adults. Several investigators have reported the psychosocial benefits of corrective surgery for adults with strabismus [1,

Table 6 Preoperative and postoperative utility values, quality-adjusted life years (QALYs) gained by the surgical intervention, yen/QALY, and $/QALY of the participants

	CS (n = 141)	NCS (n = 52)	P value	Total (n = 193)
Utility				
Preoperative	0.75 ± 0.32	0.80 ± 0.25	0.271	0.76 ± 0.31
Postoperative	0.80 ± 0.30	0 86 ± 0.20	0.108	0.82 ± 0.28
Utility gained	0.05 ± 0.15	0.06 ± 0.16	0.637	0.05 ± 0 15
QALYs gained	0.90 ± 2.60	1.25 ± 3.59	0.530	0 99 ± 2 89
Cost (yen)	119,407 ± 25,879	132,398 ± 41,851	0.718	124,926 ± 32,395
Yen/QALY	132,396 ± 54,003	106,326 ± 34,420	0.375	125,630 ± 41,728
$/QALY	1,373 ± 561	1,103 ± 358	0.375	1,303 ± 434

Results are expressed as mean ± SD

CS concomitant strabismus, *NCS* noncomitant strabismus

P value indicates that there were no statistically significant differences between the CS and NCS groups (Wilcoxon signed rank test)

Table 7 Factors associated with postoperative utility of the participants

	Univariate analysis			Multivariate analysis	
	β Coefficient (95% CI)	r	P value	β Coefficient (95% CI)	P value
Age	−0.005 (−0.007 to −0.00)	0.303	<0.001	−0.004 (−0.006 to −0 001)	0.004
Sex	0.018 (−0.061 to 0.10)	0.033	0.650	0.057 (−0.02 to 0.134)	0.147
Type of strabismus	−0.008 (−0.07 to 0.05)	0.02	0.787	−0.011 (−0.071 to 0.049)	0 716
Cure grade	0.019 (−0.01 to 0.05)	0 095	0 194	0.014 (−0.013 to 0.042)	0.303
VFQ-25 composite score	0.004 (0.001 to 0.01)	0.187	0.035	0.001 (−0.003 to 0.005)	0 679
SF-8 PCS	0.01 (0.005 to 0.02)	0.252	<0.001	0.005 (−0.002 to 0.012)	0.131
SF-8 MCS	0.00 (−0.005 to 0.01)	0.006	0.93	0.001 (−0.005 to 0.006)	0.791

CI confidence interval, *r* Pearson's product-moment correlation, *VFQ-25* Visual Function Questionnaire-25, *SF-8* 8-Item Short-Form Health Survey, *PCS* physical component summary, *MCS* mental component summary

Table 8 Cost-utility sensitivity analysis

Yen/QALY	CS (n = 141)	NCS (n = 52)	Total (n = 193)
Base case	132,396	106,326	125,630
Varying discount rate (%)			
0	76,628	61,175	72,882
5	177,651	141,824	168,965
Varying costs			
Increased by 25%	165,843	132,398	157,734
Decreased by 25%	99,505	79,439	94,641
Varying utility gain			
Lower 95% CI	207,976	171,759	197,808
Upper 95% CI	97,407	80,444	92,644
Varying duration of alignment (years)			
10	355,989	289,174	338,584
20	204,928	166,465	194,908

CS concomitant strabismus, *NCS* noncomitant strabismus, *CI* confidence interval

11, 12]. The SF-8 is a survey to assess general health-related QOL, and therefore, may not be sensitive enough to evaluate ocular diseases. Our results, however, confirmed these previous findings by using standard tools to assess vision-associated and general health status. Postoperatively, all the VFQ-25 subscale scores and the SF-8 physical and mental component summary scores showed statistically significant improvement.

Another method adopted in this study was utility assessment, which summarizes QOL status as a single number. We estimated the mean utility of strabismus adults to be 0.76 ± 0.31 by the time trade-off method, which was comparable to that previously reported by Beauchamp and associates [19]. The interpretation of this utility is that patients expecting to live 10 more years would give up, on an average, 2.3 years of that time to be free from strabismus. Although several methods are available to measure utility, the time trade-off method incorporates the quantity of lifetime directly into the utility measure, which some researchers believe makes it a preferred method of measurement [24, 25]. Thus, the time trade-off method is accepted as a formal method for quantifying the relative impact of a given health state or disease on a patient's life [25–27].

Utility assessment by the time trade-off method enables comparisons to be made across different medical conditions. For example, the preoperative results from surgical patients in the present study (mean utility 0.76) are comparable to those of ophthalmic and nonophthalmic conditions: diabetic retinopathy with 20/20–20/25 visual acuity in the better-seeing eye, 0.86; age-related macular degeneration with 20/20–20/25 visual acuity in the better-seeing eye, 0.84; unilateral amblyopia with 20/80 in the amblyopic eye, 0.83; mild stroke, 0.88; moderate post-myocardial infarction, 0.80; and early-stage prostate cancer, 0.72 [25–27].

We also measured the utility gain associated with strabismus surgery in adults, which was 0.05 on average. The utility gain in our study appears to be smaller than that reported by Beauchamp and associates [19] (mean utility gain 0.12). The reasons for this discrepancy are unclear; however, the result of the cost-utility analysis in our study (1,303 $/QALY) based on the cost model for strabismus surgery and the measured utility gain was comparable to that reported by Beauchamp and associates (1,632 $/QALY). This is assumed to result from the relatively low medical costs in Japan when compared to those in the United States. Treatments with an associated incremental cost-utility of <50,000 $/QALY are generally considered cost-effective [25–27]. Therefore, considering cost, our study demonstrated that strabismus surgery in adults is very cost-effective.

However, the results of this study raise several issues. One is whether the improved utility measured shortly after surgical intervention (3 months after the surgery) can be sustained. In the base model of our study, the utility gain was assumed to last until the end of the remaining life expectancy. The effect of surgical alignment, however, might not be maintained for a lifetime since 15.0% of patients in our study had previous surgery for the correction of strabismus. Sensitivity analysis revealed that the cost per QALY was substantially increased when the duration of alignment was limited to 10 years. On the other hand, Coats and associates [13] reported that adults with strabismus tend to postpone surgical intervention by 19.9 years on average. If the effect of surgical alignment were maintained for a long time, strabismus surgery performed at a younger age would be more cost-effective, given the relatively long life expectancy. Long-term postoperative data are necessary to evaluate the sustainability of the utility gain. Caution should also be exercised as the data of strabismus surgery in adults in the current study do not directly translate for strabismus in children. Although several authors reported the social and emotional impact of strabismus on QOL in children [30, 31], the cost-effectiveness evaluation of strabismus surgery in children requires circumspection, considering the difficulties in summarizing their health status.

In conclusion, by using standard tools to assess vision-associated and general health status, we confirmed the psychosocial benefits of corrective surgery for adults with strabismus. Our study concurrently demonstrated that strabismus surgery in adults is very cost-effective.

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Appendix

The Strabismus Surgery Group in Japan. The following individuals participated in this study.

Central Unit and Writing Committee

National Institute of Sensory Organs, National Tokyo Medical Center, Tokyo: Keiko Fujiike, Yoshinobu Mizuno, Masakazu Yamada.

National Institute of Public Health: Yoshimune Hiratsuka.

Clinical sites

Niigata University Medical and Dental Hospital, Niigata: Atsushi Miki, Rie Shirai.

Jichi Medical University, Shimotsuke: Shinji Makino, Kozue Hozawa.

National Hospital Organization Tokyo Medical Center, Tokyo: Tomoko Katsuta, Shin Hatou.

Hamamatsu University School of Medicine, Hamamatsu: Miho Sato, Akiko Hikoya, Yuka Maruyama-Koide, Yoko Tsuchiya, Risako Inagaki, Setsuko Masaki, Mitsuko Anma, Mai Asano, Megumi Washiyama.

Yagasaki Eye Clinic, Ichinomiya: Teiji Yagasaki, Hayako Matsuura, Yuko Ota, Noriko Ito, Kaori Muraguchi, Momoyo Oga.

Shohzankai Medical Foundation Miyake Eye Hospital, Nagoya: Sampei Miyake, Ken-ichiro Natsume, Kurumi Kawakami, Taeko Takada.

Nagoya University School of Medicine: Yoshiko Takai, Kiyoko Ukai.

Osaka University Medical School, Osaka: Takashi Fujikado, Kenji Matsushita, Hiroshi Shimojyo, Sanae Asonuma.

Hyogo College of Medicine, Nishinomiya: Akiko Kimura, Chigusa Aihara, Maki Tanaka.

Matsuyama Red Cross Hospital, Matsuyama: Ichiro Shimamura.

Social Insurance Chukyo Hospital, Nagoya: Yoshimi Oya, Mariko Maeda.

Tsukuba Memorial Hospital, Tsukuba: Yuka Sato, Kousuke Taki.

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Clinical Features of Anterior Segment Dysgenesis Associated With Congenital Corneal Opacities

Chika Shigeyasu, MD, Masakazu Yamada, MD, PhD, Yoshinobu Mizuno, MD, Tadashi Yokoi, MD, Sachiko Nishina, MD, PhD, and Noriyuki Azuma, MD, PhD

Purpose: Anterior segment dysgenesis is one of the main causes of congenital corneal opacities. In this study, we investigated the clinical features and visual outcomes of patients with anterior segment dysgenesis in a large number of cases.

Methods: The medical records of patients with congenital corneal opacities in relation to anterior segment dysgenesis seen in the National Center for Child Health and Development, Japan, between April 2002 and October 2009, were retrospectively studied.

Results: Records of 220 eyes of 139 patients were reviewed. Mean follow-up period was 5 years. Clinical diagnoses were Peters anomaly (72.7%), anterior staphyloma (11.4%), Rieger anomaly (7.7%), sclerocornea (6.4%), and others (1.8%). Visual acuity was measured in 61 patients. The best-corrected visual acuity in the better eye of bilaterally involved patients was 20/60 to 20/1000 (low vision according to the *International Classification of Diseases, Ninth Revision, Clinical Modification*) in 43.2% and less than 20/1000 (legally blind) in 24.3%. Fundus examination was performed in 82 eyes, and disorders were seen in 12 (12 of 82; 14.6%). Systemic abnormalities were present in 35 patients (35 of 139; 25.2%); a family history was present in 5 patients (5 of 139; 3.6%). Of the 160 eyes of 109 patients with Peters anomaly, 51 patients (51 of 109; 46.8%) had bilateral Peters anomaly, 30 (30 of 109; 27.5%) had fellow eyes that were normal, and 28 (28 of 109, 25.7%) showed other abnormal ocular findings in the fellow eye.

Conclusions: Anterior segment dysgenesis shows diverse clinical features, various severities of corneal opacities, and visual outcomes. Further understanding of the disease as an abnormality during embryogenesis and neural crest cell differentiations may be required.

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From the Division for Vision Research, National Institute of Sensory Organs, National Hospital Organization Tokyo Medical Center, Tokyo, Japan; and Department of Ophthalmology, National Center for Child Health and Development, Tokyo, Japan.
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Reprints: Chika Shigeyasu, Division for Vision Research, National Institute of Sensory Organs, National Hospital Organization Tokyo Medical Center, 2-5-1 Higashigaoka, Megurao-ku, Tokyo 152-8982, Japan (e-mail: shigeyasuchika@kankakuki.go.jp).

Key Words: anterior segment dysgenesis, congenital anomaly, cornea, Peters anomaly, visual impairment

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The causes of congenital corneal opacities (CCOs) are diverse. CCO can be genetic, glaucomatous, infectious, traumatic, developmental, metabolic, idiopathic, or toxic. Furthermore, these causes can also overlap.[1–3] When we consider the congenital causes, indicating that the corneal opacity exists in a neonate, one of the main causes, of CCO is anterior segment dysgenesis (ASD). A number of these cases are bilaterally involved and are also accompanied by other ocular malformations, sometimes with complex systemic diseases.[4] However, only a few reports concerning these abnormalities in series with a large number of cases are present.[1,5] This is because of the difficulty in performing an epidemiological study that samples a large number of newborns. Furthermore, making a precise diagnosis of a rare entity such as ASD is difficult.

ASD is induced by abnormalities during embryogenesis and neural crest cell differentiations.[6–13] Previously, ASD was called anterior chamber cleavage syndrome[12] or mesodermal dysgenesis of the iris and cornea.[14] Because it is now known that no development of a cleavage plane as the anterior segment forms and differentiates occurs[8] and because no mesoderm is involved,[7] these terms have been deemed inappropriate. Mutations in the ASD genes, *PAX6*, *PTX2*, *FOXC1*, *FOXE3*, and *CYP1B1*, have been identified.[15,16] Investigators have suggested various ASD classifications based on embryological contribution,[7] developmental arrest,[9] neural crest proliferation and migration patterns,[10] neural crest origin,[11] and anatomical findings.[12] ASD classification is sometimes complicated because it is not unusual that dysgenesis exists not only alone but also in combination with other disorders. In this study, we investigated the clinical features and visual outcomes of ASD-associated CCO in a large number of patients. We also reviewed the classification of ASD[3,6–13,15,17,18] and compared the diagnosis of both eyes of patients with Peters anomaly in 1 eye to study ASD overlap.[19–21]

SUBJECTS AND METHODS

We retrospectively reviewed the computerized medical records of all patients with ASD-associated CCO seen at the National Center for Child Health and Development (Tokyo, Japan) between April 1, 2002, and October 31, 2009.

The data were collected from computerized medical records, entering the diagnosed disease name as a key word, and all the medical records were reviewed again. The adult patients who had ASD-associated CCO diagnosed when they were younger at the former National Children's Hospital (from 1965 to March 2002) who came to the National Center for Child Health and Development for the first time were also included. In this study, ASD cases without the risk of emerging CCO and congenital aniridia were excluded. We evaluated laterality, ASD type, visual outcome, location of opacity, posterior segment abnormalities, systemic diseases, family history, and clinical course of the disorder.

Laterality (unilateral or bilateral) was diagnosed only by the existence of ASD, and other ocular findings were excluded. ASD type was diagnosed by slit-lamp examination and, when possible, with the assistance of ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT). Visual outcomes were measured considering the child's age and mental development. Picture tests were used for preverbal children. In older children, angular vision using Landolt rings followed by cortical vision was measured and converted to Snellen visual acuity. Corneal opacity location was categorized into 5 groups: diffuse, central, center to periphery, peripheral opacity, and other (including minimal corneal involvement and location not classifiable). Posterior segment abnormalities were diagnosed by clinical examination, using the slit lamp and funduscope, with the help of B-mode echography when the posterior segment was invisible because of CCO. Records of systemic disease and family history from interviews during the clinical course of the child's condition were reviewed. For a better understanding of ASD overlap, we analyzed diagnosis of both eyes of patients with Peters anomaly to observe differences in ASD diagnosis between the eyes.

RESULTS

Medical records of 220 eyes of 139 patients with ASD-associated CCO were reviewed. Among the patients, 68 were men (109 eyes) and 71 were women (111 eyes). Age at the first examination ranged from 0 months to 25 years (mean, 1.2 years; SD, 2.7). The mean follow-up period was 5 years (range, 0 months to 21 years).

Eighty-one patients (162 of 220 eyes; 73.6%) had bilateral corneal opacities and 58 (58 of 220 eyes; 26.4%) had unilateral ones. Clinical diagnosis was as follows: Peters anomaly in 160 eyes (72.7%), anterior staphyloma in 25 eyes (11.4%), Rieger anomaly in 17 eyes (7.7%), sclerocornea in 14 eyes (6.4%), and other (of unknown origin) in 4 eyes (1.8%) (Fig. 1).

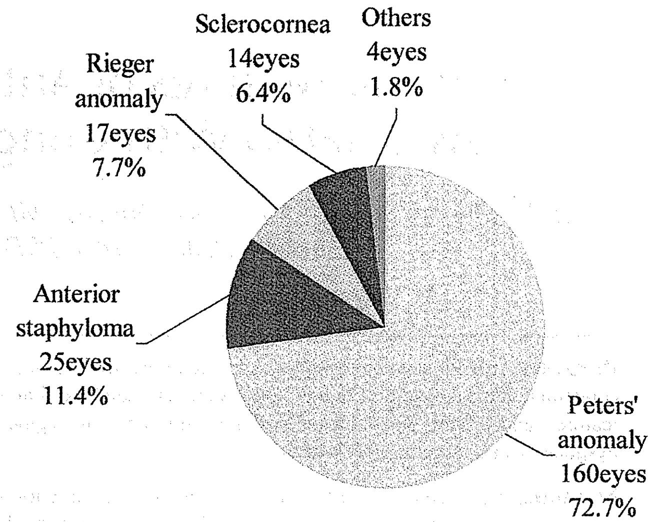

FIGURE 1. Clinical diagnosis of ASD with CCO (n = 220 eyes).

Diagnosis was made by slit-lamp examination with UBM and AS-OCT assistance in cases of severe corneal opacity. Figure 2 shows the slit-lamp photograph and corresponding image of UBM and AS-OCT in patients with bilateral Peters anomaly. The iridocorneal angle structure can be seen in detail.

Visual acuity was measured in 98 eyes of 61 patients (37 bilateral and 24 unilateral cases). Table 1 shows the best-corrected visual acuity of the eyes in bilateral and unilateral cases, and Table 2 shows the visual acuity ranges based on the better eye. The best-corrected visual acuity in the better eye of bilaterally involved patients was lower than 20/60 (low vision according to the *International Classification of Diseases, Ninth Revision, Clinical Modification*) in 43.2% and 20/1000 or worse (legally blind) in 24.3%. In total, 67.5% of patients with bilateral CCO had visual disability diagnosed.

Corneal opacity was diffuse in 48.6% of eyes, central in 17.7%, and peripheral and center to peripheral in approximately 10% each (Table 3). Of the 170 eyes of patients with corneal opacity whom we were able to follow-up, 142 (83.5%) showed no noticeable change and 28 (16.5%) showed a slight improvement. Improvement of the corneal opacity was mostly seen in patients with Peters anomaly.

Fundus examination was performed using the funduscope in 82 eyes, and fundus disorders were seen in 12. However, 138 eyes could not be examined by funduscope because of haziness. Among those 138 eyes, 125 were without major disorders, as examined by B-mode echography (Table 4). The most common disorders were persistent fetal vasculature in 4 eyes, followed by coloboma, chorioretinal atrophy, and optic nerve hypoplasia (Table 5).

Systemic abnormalities were present in 35 patients (25.2%). Multiple deformations, such as chromosome abnormality, hydrocephalus, polysyndactyly, and syndactylia, were seen in 16 patients, followed by cardiovascular disease in 5, neurologic disease (including brain hypoplasia, mental retardation, cerebral palsy, and seizure) in 5, craniofacial disease in 3 (cleft lip and palette, macroglossia and oral tumor, and dental hypoplasia), thyroid disease in 2, urinary disease in 2, and otologic disease (deafness and preauricular appendage) in 2 (Table 6). Axenfeld–Rieger syndrome, which is characterized by components of the ocular symptoms of Axenfeld anomaly and Rieger anomaly, and nonocular symptoms of Rieger syndrome were seen in 4 patients. There was a family history of ocular disorders in 5 patients (3.6%); 4 patients had a family history of Peters anomaly and 1 had a history of anterior staphyloma.

Of the 220 eyes of 139 patients in this study, we diagnosed Peters anomaly in 160 eyes of 109 patients. We reviewed the condition of the fellow eye among these 109