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CLINICAL STUDY

Validity of EuroQOL-5D, time trade-off, and standard gamble for age-related macular degeneration in the Singapore population

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Abstract

Background/aims **Utility values of age-related macular degeneration (AMD) in Asian patients are unknown. This study aims to assess utility values and construct validity of the EuroQOL-5D (EQ-5D), time trade-off (TTO), and standard gamble (SG) instruments in the Singapore multi-ethnic AMD population.**

Methods **Cross-sectional, two-centre, institution-based study. Visual acuity (VA), clinical AMD severity, and utility scores on the EQ-5D, TTO, and SG were obtained from 338 AMD patients. VA was analysed in terms of the better-seeing eye (BEVA), worse-seeing eye (WEVA), and weighted average of both eyes (WVA). We evaluated SG on the perfect health-death (SG(death)) and binocular perfect vision-binocular blindness (SG(blindness)) scales. Construct validity was determined by testing *a priori* hypotheses relating the EQ-5D, TTO, and SG utility scores to VA and clinical AMD severity.**

Results **The mean utilities on the EQ-5D, TTO, SG(death), and SG(blindness) were 0.89, 0.81, 0.86, and 0.90, respectively. EQ-5D scores correlated weakly with BEVA, WEVA, and WVA (Pearson's correlation coefficients −0.291, −0.247, and −0.305 respectively, $P<0.001$ for all). SG(death) and SG(blindness) demonstrated no correlation with BEVA, WEVA, or WVA (Pearson's correlation coefficients, range −0.06 to −0.125). TTO showed weak association only with WEVA and WVA (correlation coefficients −0.237, −0.228, $P<0.0001$), but not with BEVA (correlation coefficient −0.161). Clinical AMD severity correlated with EQ-5D and SG(death), but not with TTO and SG(blindness) ($P=0.004$, 0.002, 0.235, and 0.069, respectively).**

Conclusions **AMD has a negative impact on utilities, although utility scores were high compared with Western cohorts. EQ-5D, TTO, and SG showed suboptimal construct validity, suggesting that health status utilities may not be sufficiently robust for cost-utility analyses in this population.**

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Introduction

Age-related macular degeneration (AMD) is a progressive ocular disorder characterised by macular atrophy and impairment of central visual function. It predominantly affects individuals 60 years or older,[1] and its epidemiologic significance cannot be underestimated, with 2 million Europeans and 1.25 million Americans suffering from this disease.[2] The neovascular form of AMD is a leading cause for visual morbidity and blindness worldwide.[3]

In the last decade, various medical treatments for neovascular AMD have been developed, for example, verteporfin photodynamic therapy, pegaptanib, and ranibizumab. However, these interventions are costly and require significant patient commitment to multiple treatment

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visits. Consequently, the extent to which visual morbidity experienced by the patient is sufficiently severe to necessitate significant treatment expenditure and motivation has been questioned in recent years. The evaluation of trade-offs between patient preferences and disease-related morbidity *vs* treatment costs and morbidity is embodied in the concept of 'value-based medicine'.[4] Value-based medicine was developed by Brown and associates,[4] and refers to medical care based on cost-utility, that is, the principle that the preferred treatment intervention is one which confers the greatest gain in patient-reported health-related quality of life (QOL).[4] A cost-utility analysis has been undertaken for intravitreal ranibizumab in an American population.[2,4] Utility scores may be assessed on single-attribute methods such as the time trade-off (TTO) and standard gamble (SG) methods, or multi-attribute instruments such as the EuroQOL-5D (EQ-5D),[5,6] and can be used to calculate quality-adjusted life years and cost per quality-adjusted life year in health-care economic analyses on resource allocation.

As utility values are population-specific, cost-benefit analyses using utility instruments need to be evaluated in the population of interest.[7–9] To the best of our knowledge, no studies have examined these instruments for AMD in Asian populations. Assessment of population-specific utility values for AMD is of economic relevance in many Asian health-care systems, owing to rising health-care costs and resource allocation challenges, especially with the high prevalence of heart disease and cancers. The aims of our study were to (1) determine the utility values of AMD patients in Singapore on standardised preference-based utility instruments (EQ-5D, TTO, and SG) and (2) evaluate the construct validity of these instruments based on *a priori* hypotheses relating the utilities with clinical parameters. In eye disease, construct validity refers to the ability of a health status instrument to discriminate across different levels of disease severity or visual disability, by demonstrating good correlation with well-established or logically related indices of disease or vision function.

Materials and methods

Study cohort

This was a cross-sectional study of consecutive AMD patients attending outpatient ophthalmology clinics in two Singapore tertiary general hospitals (Alexandra Hospital and Tan Tock Seng Hospital) from April 2006 to December 2007. Eligible patients had dry or wet AMD in one or both eyes, were $\geq$40 years of age, and could give informed consent. We excluded patients with significant ocular comorbidities in either eye (eg, significant cataract, uncorrected refractive error, glaucoma, diabetic retinopathy, or myopic macular degeneration), and patients with hearing, psychiatric, or cognitive diseases. Eligible patients who provided informed written consent were included. This study was approved by the hospital Institutional Review Boards and adhered to the tenets of the World Medical Association's Declaration of Helsinki.

Data collection

The interviewer first met with study clinical investigators and interpreters to rehearse questionnaire administration and reduce linguistic and semantic discrepancies. A trained interviewer administered the 15-min questionnaire to eligible patients before the outpatient consultation to reduce consultation bias. Where necessary, the questionnaire was verbally translated by the same interviewer into the patient's preferred spoken language, that is, English, Mandarin, or Malay. The interviewer encouraged the patients to seek clarification if they were unable to understand the questionnaire.

The questionnaires surveyed socioeconomic data, time from initial visual loss to time of interview, personal history of ocular and medical conditions, followed by the utility questions.

Health status and health-related QOL utility instruments

Three preference-based utility instruments (EQ-5D, TTO, and SG) were selected based on their applicability in health economic analyses. The National Institute of Clinical Excellence and National Institute of Health recognise the use of health status measures such as the EQ-5D in comparative health-care economic analyses.[10]

The EQ-5D is a generic QOL instrument widely used to measure generic health status, with psychometric validity for many diseases. The succinct questionnaire structure facilitates easy administration. The EQ-5D has been validated in Singapore patients with rheumatic disorders and Parkinson's disease.[11,12] It comprises a 5-dimension health descriptive system: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, where patients are asked to rate their health problems at three levels: none, moderate, or extreme. An index utility score can be derived from the responses in the five dimensions, ranging from -0.59 for worst possible health state to 1.00 for perfect health. There are several country-specific EQ-5D values available. As no population-based scores are available for the Singapore population, we used the scores from the general UK population.[13]

The assessment of TTO and SG utilities was based on a standardised methodology.[14,15] Both TTO and SG are

widely used methods of utility assessment, showing construct validity with visual acuity (VA) in other AMD studies.[16–18] Assessment of TTO utility used the anchors of 'death' and 'perfect binocular vision'. We asked participants the number of years they expected to live, and the number of years of their expected remaining life they were willing to trade off for a treatment giving perfect binocular vision. The TTO utility was calculated from the equation: TTO = 1.0 − (time traded in years/estimated number of years of remaining life). By convention, utilities vary from 0.0 (death) to 1.0 (perfect binocular vision).

We assessed the SG in two ways:[15] first, based on the conventional policy scale for cost-utility assessments, with 'perfect health' (defined as ideal health, including perfect binocular vision) as the upper anchor and 'death' as the lower anchor, and by using a modified scale with 'binocular blindness' as the lower anchor and 'perfect binocular vision' as the upper anchor. The policy scale SG (SG(death)) was elicited by asking patients what risk of immediate death they would accept with a hypothetical technology before refusing treatment in return for a state of perfect health. The modified scale SG (SG(blindness)) was assessed by asking patients the risk of immediate binocular blindness they would be able to accept before refusing treatment, in return for a state of perfect vision in both eyes. The SG utility was calculated: SG = 1.0 − (risk of death or binocular blindness a patient is willing to accept). SG scores range from 0.0 (death or binocular blindness) to 1.0 (perfect health or perfect binocular vision).

Clinical examination

Patients underwent a comprehensive ophthalmic examination, including habitual distance Snellen VA testing, slit-lamp biomicroscopy, and dilated fundal examination with a 78-dioptre lens. Habitual VA more accurately reflects the patient's day-to-day visual function status and is preferred to best-corrected VA. Snellen VA was scored and converted to a logarithm of the minimum angle of resolution (logMAR) score.

Fundus photographs were taken with a mydriatic camera (FF450plus, Carl Zeiss Meditec, Jena, Germany). An examiner with retinal subspecialty training clinically assessed the fundus and correlated this with the fundus photographs. Clinical AMD severity was evaluated by a 5-level categorisation system: dry/normal, dry/dry, wet/normal, wet/dry, and wet/wet. The examiner was masked to the patient's responses to the utility questions and VA findings. An eye with drusen or retinal pigment epithelial abnormalities was considered to have dry AMD. Wet AMD was defined if choroidal neovascularisation, subretinal haemorrhage, serous or haemorrhagic pigment epithelial detachment were present on fundal fluorescein angiography. Geographic atrophy (advanced dry AMD) was considered equivalent to neovascular AMD. Compared with the grading system used by Mackenzie *et al*,[19] which categorised AMD severity based on specific combinations of exudative and non-exudative features, the simpler grading system used in our study was deliberately intended to rank severity levels in a manner which would be convenient for clinical practice.

Statistical analyses

Descriptive methods were used to characterise the sociodemographic and clinical characteristics and health status utilities of the study population. The construct validity of the EQ-5D, TTO, and SG was assessed by testing *a priori* hypotheses relating utility scores with clinical indices of disease severity. Current literature shows that utility measures (eg, TTO and SG) correlate better with disease indices than generic health status instruments (eg, EQ-5D),[5,16,18–21] and clinical AMD severity correlates poorly on utility measures and EQ-5D.[22,23] Therefore, we hypothesised that (1) EQ-5D would correlate weakly to moderately well with VA and clinical AMD severity, (2) TTO and SG would show a moderate to strong correlation with VA, but null to weak correlation with clinical AMD severity.

We analysed VA in the better-seeing eye (BEVA), worse-seeing eye (WEVA), and weighted average of both eyes (WVA) as separate variables of interest. The logMAR WVA was based on a 75% contribution by BEVA and 25% contribution by WEVA.[24]

Associations between the continuous variables were examined using the Pearson's correlation coefficient; coefficients of >0.5, >0.35–0.50, >0.20–0.35, and ≤ 0.2 were considered strong, moderate, weak, or no correlation, respectively. Associations between utility scores and clinical AMD severity were analysed using one-way analysis of variance. All statistical tests were two-sided and $P<0.05$ was considered statistically significant. Data were analysed with SAS (Version 9.2 for Windows, Cary, NC, USA).

Results

Of 366 eligible patients, we excluded 28 patients (8 glaucoma, 12 significant cataract, 3 diabetic macular oedema, 3 proliferative diabetic retinopathy, 1 dementia, and 1 hearing difficulty). Three hundred and thirty-eight patients (92.6% participation rate) were included. Two hundred and seven patients (61.2%) were male. The mean age of all subjects was 68.1 ± 9.4 years. Three hundred and three patients (89.6%) were Chinese. The

Table 1 Sociodemographic, clinical, and utility score characteristics

	N *(%)*
Sociodemographic characteristics	
Number of participants	338
Mean age (years)	68.1 ± 9.4 (range 48–92)
Gender	
Male	207 (61.2%)
Female	131 (38.8%)
Ethnicity	
Chinese	303 (89.6%)
Malay	5 (1.8%)
Indian	15 (4.3%)
Other ethnicity	15 (4.3%)
Housing type	
1–3 room apartments	68 (20.1%)
4–5 room apartments	109 (32.3%)
Condominium/landed property	161 (47.6%)
Number of persons staying in the same house as patient	
Living alone	99 (29.3%)
1–2	153 (45.3%)
⩾3	86 (25.4%)
Educational attainment	
No formal education	100 (29.6%)
Primary 6	77 (22.8%)
A level/diploma	139 (41.1%)
University degree	22 (6.5%)
Employment status	
Employed	96 (28.4%)
Unemployed	242 (71.6%)
Personal monthly income (Singapore dollars, SGD)[a]	
0–999	49 (14.5%)
1000–1999	28 (8.3%)
2000–2999	12 (3.6%)
⩾3000	24 (7.1%)
Undeclared	225 (66.6%)
Family history of eye disorders	
None	292 (86.4%)
Age-related macular degeneration	4 (1.2%)
Cataract	32 (9.5%)
Diabetic retinopathy	5 (1.5%)
Glaucoma	5 (1.5%)
Clinical	
Mean duration of vision loss (years)	1.47 ± 1.80
Concomitant mild ocular comorbidity	
Cataract	35 (10.4%)
Glaucoma	2 (0.6%)
Diabetic retinopathy	9 (2.7%)
Mean visual acuity	
Better eye (BEVA)	0.20 ± 0.23
Worse eye (WEVA)	0.65 ± 0.72
Weighted visual acuity (WVA)	0.31 ± 0.31
Clinical severity of age-related macular degeneration in both eyes	
Dry-normal	35 (10.4%)
Dry-dry	178 (52.7%)
Dry-wet	31 (9.2%)
Wet-normal (or geographic atrophy-normal)	64 (18.9%)
Wet-wet (or geographic atrophy-geographic atrophy, or geographic atrophy-wet AMD)	30 (8.9%)
Utility scores	
Mean utilities	
EuroQOL-5D (EQ-5D) index	0.89 ± 0.14
Time trade-off (TTO)	0.81 ± 0.23
Standard gamble (SG) for blindness	0.91 ± 0.21
Standard gamble (SG) for death	0.86 ± 0.26

[a]One SGD equivalent to ~0.70 USD at the time of study.

Table 2 Response distribution of EuroQOL-5D (EQ-5D) domains

	None, n *(%)*	*Moderate,* n *(%)*	*Extreme,* n *(%)*
Mobility	281 (83.1%)	57 (16.9%)	0 (0%)
Self-care	333 (98.5%)	5 (1.5%)	0 (0%)
Usual activities	276 (81.6%)	61 (18.1%)	1 (0.3%)
Pain/discomfort	256 (75.7%)	82 (24.3%)	0 (0%)
Anxiety/depression	268 (79.3%)	65 (19.2%)	5 (1.5%)

mean duration of self-reported visual loss was 1.47 ± 1.80 years. Mean BEVA, WEVA, and WVA were 0.195 ± 0.228, 0.650 ± 0.722, and 0.309 ± 0.309, respectively. Mean EQ-5D, TTO, SG(death), and SG(blindness) utilities were 0.89 ± 0.14, 0.81 ± 0.23, 0.86 ± 0.26, and 0.91 ± 0.21, respectively. Table 1 summarises the sociodemographic, clinical, and VA data.

Patient responses on the EQ-5D categories are shown (Table 2). Moderate to extreme degrees of pain/discomfort and anxiety/depression were reported by 24.3% and 20.7% of participants, respectively. In addition, moderate to extreme difficulty with usual activities, mobility, and self-care were reported by 18.4%, 16.9% and 1.5% of participants, respectively.

Although the EQ-5D and SG questions yielded 100% response rates, 44 patients (13.0%) declined to indicate a risk value for the TTO question. Non-respondents cited the following reasons: (1) the discussion of death in general was taboo (20 patients, 45%) and (2) the issue of giving up years of life was objectionable to religious beliefs (11 patients, 25%). Thirteen patients (29.5%) who declined did not specify any reason. Respondents and

Table 3 Pearson's correlation coefficients between clinical variables against preference-based utility scores on EuroQOL-5D, time trade-off, and standard gamble

	EQ-5D	*TTO*	*SG (death)*[a]	*SG (blindness)*[b]
Better-seeing eye visual acuity (BEVA)	−0.291*	−0.161	−0.061	−0.057
Worse-seeing eye visual acuity (WEVA)	−0.247*	−0.237*	−0.120	−0.125
Weighted visual acuity (WVA)	−0.305*	−0.228*	−0.104	−0.105

*$P < 0.001$.
[a]Conventional policy scale standard gamble utility using 'death' as the lower anchor and 'perfect health' as the upper anchor.
[b]Modified scale standard gamble utility using 'binocular blindness' as the lower anchor and 'perfect binocular vision' as the upper anchor.

Table 4 Mean preference-based utilities[a] on EuroQOL-5D, time trade-off, and standard gamble associated with patients categorised according to clinical severity of age-related macular degeneration

	Dry/normal	*Dry/dry*	*Wet/normal*	*Wet/dry*	*Wet/wet*	P-*value*[b]
EQ-5D	0.87 (0.12)	0.91 (0.11)	0.90 (0.11)	0.85 (0.18)	0.83 (0.19)	0.004
TTO	0.88 (0.19)	0.82 (0.23)	0.77 (0.19)	0.78 (0.26)	0.78 (0.26)	0.235
SG (death)	0.97 (0.12)	0.88 (0.23)	0.74 (0.31)	0.80 (0.33)	0.86 (0.29)	0.002
SG (blindness)	0.96 (0.12)	0.92 (0.12)	0.87 (0.20)	0.85 (0.27)	0.94 (0.14)	0.069

[a]Expressed as mean (SD).
[b]One-way analysis of variance (ANOVA).

non-respondents were comparable for sociodemographic and clinical characteristics except for age, which was significantly higher in non-respondents than in responders (mean age 72.3 *vs* 67.5 years, $P < 0.0001$).

Table 3 illustrates the Pearson's correlation coefficients between utilities and clinical variables. For EQ-5D, these were −0.247, −0.291, and −0.305 for WEVA, BEVA, and WVA, respectively, indicating weak associations. TTO correlated weakly with WEVA and WVA and no correlation with BEVA (Pearson's correlation coefficients −0.237, −0.228, and −0.161, respectively). SG(death) and SG(blindness) did not correlate with BEVA, WEVA, or WVA. The relationship between utility scores and AMD severity is illustrated (Table 4). Patients with more severe AMD had significantly lower utility scores on the EQ-5D ($P = 0.004$) and SG(death) ($P = 0.002$). In contrast, SG(blindness) and TTO were unable to discriminate between different levels of AMD severity ($P = 0.069$ and $P = 0.235$, respectively).

Discussion

Value-based medicine is an evidence-based analytic method to assess the value gain of various treatment interventions for AMD.[4] However, this method is based on population-specific baseline utility values determined with a validated instrument. To our knowledge, this is the first study evaluating utility values for AMD in an Asian population. This institution-based study of Singapore AMD patients showed a negative impact of AMD demonstrated using the EQ-5D, TTO, and SG utility instruments, although the scores obtained were still relatively high compared with Western cohorts. This is also the first study showing a suboptimal correlation of utilities and clinical parameters.

AMD negatively impacts QOL as determined with the EQ-5D, TTO, and SG instruments in this population. Patients with AMD were willing to take 1.9 off every 10 years of remaining life for perfect vision, and take a 14% risk of death and 10% risk of blindness in both eyes, for a treatment conferring perfect vision; this highlights the degree of visual morbidity experienced by patients. However, higher scores were generally obtained on all utility instruments in our cohort compared with Western populations, indicating a lower disease-related health and visual morbidity experienced (Tables 5 and 6). A key implication for clinical practice is that the receptiveness of the Singapore AMD population to any treatment intervention with inherent risks may be less than ideal. Treatment decisions in clinical practice may need to adopt a more conservative and individualised approach taking into account patient preferences for treatment. Our results support a trend in TTO and SG for major eye diseases (glaucoma, diabetic retinopathy, and myopia), in which utility scores are higher in Asian than in Western cohorts.[15,25–29] This is especially so for Singapore where utility scores for glaucoma and myopia are the highest reported.[25,29] Several reasons may account for the high utility scores, which indicate that patients are reluctant to give up years of life, or risk death or blindness for an effective treatment, preferring to maintain at a state of poor vision. Sociocultural factors influence the patient's overall perception of the disease, coping strategies and risk-taking behaviour.[30,31]

Table 5 Published quality of life studies assessing EuroQOL-5D (EQ-5D) in ophthalmic diseases

Study	*Disease*	*Population*	*EQ-5D*	*Visual acuity severity profile*	*Pearson's/Spearman's correlation coefficient for visual acuity*
This study ($n=338$)	AMD	Singapore	0.89	Mean BEVA: 0.20 Mean WEVA: 0.65 Mean Weighted VA: 0.31	BEVA: −0.291 WEVA: −0.247 Weighted VA: −0.305
Soubrane *et al*[6] ($n=401$)	AMD	France, Germany, Spain, UK, Canada	0.65	Mean BEVA: 0.6	Not assessed, but no association found with BEVA
Cruess *et al*[33] ($n=67$)	AMD	Canada	0.64	BEVA >20/40: 14.9% >20/80–20/40: 10.4% >20/200–20/80: 31.3% >20/400–20/200: 25.4% 20/400 or worse: 13.4%	Not assessed, but no association found with BEVA
Lotery *et al*[34] ($n=75$)	Neovascular AMD	UK	0.67	Better than 20/40 to worse than 20/400; no percentages given	Not assessed, but no association found with BEVA
Espallargues *et al*[5] ($n=209$)	AMD	UK	0.72	Mean BEVA: 1.01 Mean WEVA: 1.68	BEVA: −0.09
Clark *et al*[35] ($n=19$)	Post-operative endophthalmitis	Australia	0.66	No visual impairment (VI): 47% Unilateral VI: 47% Bilateral VI: 6%	Not assessed
Aspinall *et al*[36] ($n=72$)	Glaucoma	UK	0.76	78% with VA better than 6/12 in both eyes	Not assessed, but significant association found with VA ($P<0.01$)
Kobelt *et al*[37] ($n=199$)	Glaucoma	Sweden	0.80	Mean BEVA: 0.63 Mean WEVA: 0.87 Weighted VA: 0.80	Not assessed, but no association found
Lloyd *et al*[38] ($n=101$)	Diabetic retinopathy	UK	Not assessed	6/6–6/9: 67% 6/12–6/18: 13% 6/24–6/36: 10% 6/60–6/120: 7% CF–HM: 3%	Not assessed; $R^2=0.123$
Polack *et al*[39] ($n=217$)	Cataract	Bangladesh	Not assessed	BEVA <6/24–6/60: 26% <6/60–3/60: 19% <3/60–>PL: 14% PL: 41%	Not assessed
Polack *et al*[40] ($n=196$)	Cataract	Kenya	Not assessed	BEVA <6/24–6/60: 39.8% <6/60–3/60: 20.9% <3/60–>PL: 18.4% PL: 20.9%	Not assessed
Datta *et al*[41] ($n=306$)	Cataract	UK	0.73	Mean BEVA: 0.28	Standardised β: 0.01
Lengalaan *et al*[42] ($n=128$)	Visually impaired	Netherlands	0.73	Not reported	Not assessed
Rajagopalan *et al*[43] ($n=32$)	Sjögren's syndrome keratoconjunctivitis sicca	USA, Canada	0.74	Not reported	Not assessed

For example, AMD patients in this study had access to a social network (70.7% of patients lived with two or more people in the same household), which may lessen the psychological or social impact of the disease. Living arrangements have not been discussed in previous utility studies; however, the elderly in the West tend to reside alone or with only one other person.[32] Differences in the delivery of ophthalmic care may also be responsible. Another possibility may lie in patient awareness of the significant costs and compliance required of treatment, or even unawareness of the natural disease progression without treatment.

Table 6 Published quality of life studies assessing time trade-off (TTO) and standard gamble (SG) in age-related macular degeneration (AMD)

Study	*Mean visual acuity*	*TTO*	*Anchors*	*Correlations*	*SG*	*Anchors*	*Correlations*
This study (2009) ($n=338$)	BEVA: 0.19 WEVA: 0.65	0.81	Perfect vision/death	None found with BEVA, WEVA, AMD severity	0.91	Perfect health/death	AMD severity
					0.86	Perfect vision/blindness	None found with BEVA, WEVA, AMD severity
Lee *et al*[15] ($n=44$)	BEVA: 0.40	—	—	—	0.83	Perfect health/death	None examined but trend demonstrated
Espallargues *et al*[5] ($n=209$)	BEVA: 1.01 WEVA: 1.68	0.64	Perfect health/death	Weakly correlated with BEVA (Pearson's −0.21)	—	—	—
Shah *et al*[27] ($n=150$)	Not reported	0.94, 0.96, 0.80	Perfect vision/death	None found with BEVA	—	—	—
Brown *et al*[17] ($n=263$)	BEVA: 20/45	0.79	Perfect vision/death	BEVA	—	—	—
Brown *et al*[16] ($n=80$)	BEVA: 20/40	0.72	Perfect vision/death	BEVA	0.81	Perfect vision/death	BEVA

Nevertheless, the high utility values in our population may be attributed to the disease severity profile or systemic comorbidities.[5,9,16,17] Mean logMAR BEVA and WEVA in this study were 0.20 and 0.65, respectively, indicating generally less severe disease (Tables 5 and 6). Direct comparison of utilities should be approached cautiously, as scores are affected when top, bottom, or both anchors of utility instruments are changed.[15] SG was defined in other studies using a bottom anchor of death (Table 6), thus SG(blindness) (ie, perfect vision-binocular blindness) scores may not be directly comparable to other SG scores.

In this study, suboptimal correlation of EQ-5D, TTO, and SG with BEVA, WEVA, and WVA was demonstrated, and only clinical AMD severity was associated with EQ-5D and SG(death). For construct validity to be demonstrated, several clinical parameters should show strong correlation with utility scores. This has several implications. In clinical practice, the degree of visual impairment or disease severity may not sufficiently reflect the patient's functional state or preference for treatment. At the health-care policy level, utility values are likely limited in application for economic analyses.

EQ-5D is recognised for its poor responsiveness to VA loss and insensitivity in capturing impact on activities requiring good central vision, due to the generic construct of instrument domains and lack of vision-specific subscales.[5,6] Datta *et al*,[41] Aspinall *et al*,[36] and Lloyd *et al*[38] reported that EQ-5D correlated weakly in cataract, glaucoma, and diabetic retinopathy, respectively. This study supports these findings (Table 5).

BEVA was a good predictor of TTO and SG scores in previous studies (Table 6). However, Singapore AMD patients may in general be more risk averse, especially if involving ill fortune such as 'death' and 'blindness', giving a clustering effect of scores at the upper limit of the range and preventing sufficient discrimination of scores by severity of visual impairment. TTO and SG utility scores were also generally high in AMD and in other ocular conditions,[5,22,36] suggesting a limitation of these instruments.

We found significant associations between AMD clinical severity and EQ-5D or SG(death), but not for SG(blindness) or TTO. In contrast to VA measures, laterality and exudative/non-exudative categorisation of disease severity may provide more accurate stratification of disease severity than VA, as VA captures only central visual impairment. This suggests that other aspects of visual function and symptoms (contrast sensitivity, metamorphopsia, and scotomas) may be responsible for overall QOL in AMD patients.

The non-respondent rate of 13% on the TTO raises concern on its use; poor response rates with TTO were also previously reported.[44] Interestingly, non-response was not a significant problem with SG(death) and SG(blindness), possibly suggesting that requiring the patient to foretell the length of remaining life span, rather than patient acceptance of a risk of death consequent to a treatment intervention, is objectionable. A subgroup analysis (Appendix) found that non-response on TTO was associated with age and female gender; hence further studies evaluating TTO for age-related eye

disease may expect more non-response in older and female individuals.

Limitations in this study are that it is hospital based, hence the utilities may not generalise to the Singapore AMD population, which has a less severe disease profile. Second, we are unable to compare findings on the EQ-5D, TTO, and SG with outcomes on other instruments, for example, generic health status utility on the Health-utilities index 3 (HUI-3) or vision-specific functional status with the National Eye Institute Visual Function Questionnaire (NEI-VFQ). We did not include these questionnaires due to likely interviewee fatigue. However, only the HUI-3, but not the NEI-VFQ, is suitable for cost-utility analyses. Given the generally suboptimal construct validity demonstrated with clinical indicators, correlation of utilities with other non-VA clinical indicators (eg, contrast sensitivity) or proxies of disease severity such as vision-related functional status scores (eg, NEI-VFQ) may be explored.

In conclusion, AMD has a negative impact on health status of Singapore patients, although the utility values are generally higher than for Western patients. The construct validity of EQ-5D, TTO, and SG was suboptimal, and response rates on the TTO may be of concern. These results suggest that health status utilities may not be sufficiently robust for health-care economic analyses in this population.

Summary

What was known before

- Measures of health-related quality of life of AMD patients in Western populations.
- Previous established instruments for health-care economic analysis valid in Western populations.

What this study adds

- Negative impact of AMD in an Asian population. Relatively high health-related quality of life of AMD patients in a multi-ethnic Asian population in Singapore.
- Generally challenging to establish the construct validity of these instruments in our population, as seen in other quality of life studies from Asia.
- Highlights need to identify other instruments to measure quality of life in Asian patients with AMD, should health-care economic evaluation dependent on quality of life measures be required in the future.

Conflict of interest

The authors declare no conflict of interest.

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Appendix

Comparison between sociodemographic and clinical variables between respondents and non-respondents on time trade-off utility instrument

	Respondents (n = *294*)	*Non-respondents* (n = *44*)	P-*value*
Age	67.5 ± 0.72	72.3 ± 1.1	<0.0001
Ethnicity			
Chinese	40 (90.9%)	263 (89.5%)	1.00
Non-Chinese	4 (9.1%)	31 (10.5%)	
Housing type			
1–3 room apartments	62 (21.1%)	6 (13.6%)	0.457
4–5 room apartments	95 (32.3%)	14 (31.8%)	
Condominiums/landed property	137 (46.6%)	24 (54.6%)	
Number of persons staying in the same house as the patient			
Living alone	86 (29.3%)	13 (29.6%)	0.944
1–2	134 (45.6%)	19 (43.2%)	
≥3	74 (25.2%)	12 (27.3%)	
Educational attainment			
No formal education	81 (27.6%)	19 (43.2%)	0.176
Primary 6	68 (23.1%)	9 (20.5%)	
A level/diploma	126 (42.8%)	13 (29.6%)	
University degree	19 (6.5%)	3 (6.8%)	
Personal monthly income[a]			
0–999	40 (13.6%)	9 (20.5%)	0.677
1000–1999	26 (7. 7%)	2 (4.6%)	
2000–2999	10 (3.4%)	2 (4.6%)	
≥3000	21 (7.1%)	3 (6.8%)	
Undeclared	197 (67.0%)	28 (63.6%)	
Employment status			
Employed	87 (29.6%)	9 (20.5%)	0.210
Unemployed	207 (70.4%)	35 (79.6%)	
Family history of eye disorders			
None	250 (85.0%)	42 (95.5%)	0.060
Yes	44 (15.0%)	2 (4.6%)	
Duration of visual loss	1.50 ± 1.40	1.48 ± 1.42	0.930
Visual acuity			
Better eye (BEVA)	0.20 ± 0.23	0.22 ± 0.19	0.583
Worse eye (WEVA)	0.64 ± 0.70	0.65 ± 0.68	0.929
Weighted visual acuity (WVA)	0.30 ± 0.28	0.33 ± 0.34	0.520
Clinical severity of AMD			
Dry/normal	33 (11.2%)	2 (4.6%)	0.307
Dry/dry	156 (53.1%)	22 (50.0%)	
Wet/normal	26 (8.8%)	5 (11.4%)	
Wet/dry	56 (16.6%)	8 (18.2%)	
Wet/wet	23 (7.8%)	7 (15.9%)	

[a]One SGD equivalent to 0.70 USD at the time of study.