Original Article

Cost-Effectiveness Analysis of Non-Mydriatic Ultrawide-Field Fundus Photography versus Pharmacological Pupil Dilatation in Diabetic Retinopathy Screening Program

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Background: Diabetic retinopathy (DR) causes blindness of the population in many countries worldwide. Early detection and treatment of this disease via a DR screening program is the best way to secure the vision. An annual screening program using pharmacological pupil dilatation becomes the standard method. Recently, non-mydriatic ultrawide-field fundus photography (UWF) has been proposed as a choice for DR screening. However, there was no cost-effectiveness study between the standard DR screening and this UWF approach.

Objective: To compare the cost-effectiveness between UWF and pharmacological pupil dilatation in terms of hospital and societal perspectives.

Materials and Methods: Patients with type 2 diabetes mellitus that visited the ophthalmology clinic at Chulabhorn Hospital for DR screening were randomized using simple randomization method. The patients were interviewed by a trained interviewer for general and economic information. The clinical characteristics of DR and staging were recorded. Direct medical costs, direct non-medical costs, and informal care costs due to DR screening were recorded. Cost analyses were calculated for the hospital and societal perspectives.

Results: The present study presented the cost-effectiveness analyses of UWF versus pharmacological pupil dilatation. Cost-effectiveness analysis from the hospital perspective showed the incremental cost-effectiveness ratio (ICER) of UWF to be –13.87. UWF was a cost-effective mean in DR screening in the societal perspective when compared with pharmacologically pupil dilatation with the ICER of 76.46, under the threshold of willingness to pay.

Conclusion: The UWF was a cost-effective mean in DR screening. It can reduce screening duration and bypass post-screening blurred vision. The results suggested that UWF could be a viable option for DR screening.

Keywords: Diabetic retinopathy, Diabetic retinopathy screening, Non-mydriatic ultrawide-field fundus photography, Cost-effectiveness analysis

Received 10 November 2020 | Revised 26 February 2021 | Accepted 9 March 2021

J Med Assoc Thai 2021;104(5):818-24

Website: http://www.jmatonline.com

Diabetes mellitus is the most common chronic disease in many countries. Prevalence of diabetes mellitus patients in Thailand was 8.2% in 2011 and projected to be 9.8% in 2030, with the mean annual incremental rate of 76,000 persons per year[1]. Diabetic retinopathy (DR) is a common microvascular complication of diabetes, resulting in blindness. An annual screening program has been established in many countries to protect eye-sight with the standard method, which is pharmacological pupil dilatation and examination by ophthalmologist[2,3]. However, only 40% to 60% of American population attend this program due to inconveniences caused by the time consuming procedure and blurred vision afterward, which disturbs patients' daily activities[3].

A non-mydriatic fundus photography has now been deployed in several countries[4-9]. The images present single field at posterior pole of retina and adjacent 45 degree from the central. There is no difference between pharmacological pupil dilatation and non-mydriatic fundus photography for DR detection[7]. Moreover, non-mydriatic fundus photography provides many conveniences to the patients. They can readily resume daily activities

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How to cite this article:

Wongvisavavit R, Nantajit D, Phodha T. Cost-Effectiveness Analysis of Non-Mydriatic Ultrawide-Field Fundus Photography versus Pharmacological Pupil Dilatation in Diabetic Retinopathy Screening Program. J Med Assoc Thai 2021;104:818-24.

doi.org/10.35755/jmedassocthai.2021.05.12238

after the screening and there is no waiting time for pupil dilatation. A previous study comparing a non-mydriatic fundus camera and no screening of DR showed that portable non-mydriatic fundus camera is a cost-effective mean of screening for DR in isolated communities of at-risk individuals with the cost approximated to be $1.2 million for five years. Over the 10 years, 67 sight years were saved, at a cost of $3,900 per sight year and $15,000 per quality-adjusted life years (QALYs)[8]. Likewise, a study in South Africa demonstrated that non-mydriatic fundus camera is a cost-effective measure in screening and diagnosis of DR in a primary care setting. The incremental cost-effectiveness ratio (ICER) was 10,500 ZAR ($1,206) per blindness case averted with a willingness to pay threshold of 11,000 ZAR[9]. Fundus images obtained with non-mydriatic fundus camera could be considered as an effective, cost-sparing, and feasible screening tool for DR detection[9,10]. However, peripheral DR lesion detection could be missed due to the narrow degree of images.

Recently, non-mydriatic ultrawide-field fundus photography (UWF), which can image 200 degree of the retinal surface including peripheral retina that include 80% of the retina surface, has been introduced to solve this narrow field problem. The use of UWF imaging for DR screening can achieve a sensitivity of 94% and specificity up to 100%[11]. At present, the major limitation of UWF is the instrument cost. Despite superior outcomes in clinical trials, it remains unclear in terms of cost-effectiveness between the standard DR screening and this UWF approach. At Chulabhorn Hospital, both the pharmacological pupil dilatation and the UWF have been used for DR screening. Thus, the present study aimed to compare the cost-effectiveness between UWF and pharmacological pupil dilatation in both hospital and societal perspectives.

Materials and Methods

Study population

The present study included patients with type 2 diabetes mellitus who visited the ophthalmology clinic at Chulabhorn Hospital for DR screening between April 1, 2018 and July 31, 2018. The patients were informed and inquired for willingness to participate in the study. Patients were asked for consents and interviewed by a trained interviewer for general and economic information. Patients were randomized to receive either pharmacological pupil dilatation (1% tropicamide, 1% Mydriacyl®, Alcon) or UWF (Optos, Daytona, United Kingdom) using a simple randomization method. In the pharmacologically pupil dilatation group, the patients received an eye drop every five minutes. Pupil sizes were evaluated after 15 minutes. If inadequate sizes presented, drug instillation continued until full dilatation. In the UWF group, the patients received fundus photography. The fundus examination was performed by a single ophthalmologist.

Inclusion criteria:

1. Confirmed type 2 diabetes mellitus patient
2. Age older than 35 years old
3. Required a visit for DR screening

Exclusion criteria:

1. Patient failed to understand or answer the interview
2. Patient declined to join the study

Data collection

Demographic characteristics collected by the interviewer composed of age, gender, occupation, marital status, education, health insurance, and income. Clinical characteristics were received from the ophthalmologist who reported visual acuity, ocular tension, general eye examination, and DR status. The clinical characteristics of DR and staging were recorded. The information on direct medical costs (DMC) was retrieved from the hospital database including visual acuity test, slit-lamp examination, pupil dilatation procedure, mydriatic drug, and fundus photography. Patients or their caregivers were interviewed for the direct non-medical costs (DNMC) information including the costs for their transportation, meal, accommodation, and informal care cost due to DR screening. Likewise, patients or their caregivers were asked about the duration that the patients spent on the screening program and the duration from the beginning of mydriatic drug instillation to the time that the patients recovered and gained normal vision.

Data analysis

Distribution in the demographic characteristics between the patients in the pharmacologically pupil dilatation group and the UWF group were analyzed. Costs analyses were calculated for hospital and societal perspectives. All costs data were in 2018 values. The DMC were collected as charge data and converted to costs by multiplying with the cost to charge ratio for Chulabhorn Hospital, which equaled 0.64 (Chulabhorn Hospital reference). Human capital approach was deployed to estimate the

informal care costs and the indirect costs. The Gross National Income (GNI) per capita from the second quarter of 2018[12] and patient and caregiver incomes were used for time valuing. The ICER of UWF to pharmacologically pupil dilatation was analyzed using decision tree model. One-way sensitivity analysis was performed by varying the perspective and time referencing value variables of indirect costs.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was considered significant.

Ethical approval

The study was reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects, Chulabhorn Research Institute (reference number 056/2560). The data were anonymously recorded and confidentially retained.

Results

Descriptive analysis

Sixty-four patients with type II diabetes mellitus came to Chulabhorn Hospital for DR screening between April and July 2018. Table 1 presents the distribution of patients' characteristics. There were 30 males and 34 females. Patients were randomized to receive pharmacological pupil dilatation or UWF. In the pharmacological pupil dilatation group, there were 13 (40.6%) males and 19 (59.4%) females. In the UWF group, there were 17 (53.1%) males and 15 (46.9%) females. The median age in the pharmacological pupil dilatation group and the UWF group were 61 and 63 years old, respectively. Fifty percent of the patients were unemployed and more than 60% were married. More than a quarter of the patients had a bachelor's degree, 37.5% and 25% in the pharmacological pupil dilatation group and UWF group, respectively. In addition, 56.3% and 65.6% of the patients were under civil servant medical benefit scheme. Most patients' incomes in both groups were between 10,000 and 50,000 Baht, 37.5% and 43.7% in the pharmacological pupil dilatation group and the UWF group, respectively. Likewise, 78.1% and 59.4% of the patients had no DR in the pharmacological pupil dilatation and UWF groups, respectively. There was no statistically significant difference in the demographics between both groups.

Table 1. Demographic data

Characteristics	Pharmacological pupil dilatation (n=32); n (%)	Non-mydriatic UWF (n=32); n (%)	p-value*
Sex			0.45
Male	13 (40.6)	17 (53.1)	
Female	19 (59.4)	15 (46.9)	
Age (year)			0.47
<50	2 (6.3)	2 (6.3)	
50 to 59	13 (40.6)	8 (25.0)	
60 to 69	10 (31.3)	14 (43.8)	
70 to 79	7 (21.9)	6 (18.8)	
≥80	0 (0.0)	2 (6.3)	
Median (IQR)	61 (57 to 69)	63 (60 to 70)	
Occupation			0.34
Government official	10 (31.3)	12 (37.5)	
State enterprise	4 (12.5)	0 (0.0)	
Farmer	1 (3.1)	1 (3.1)	
Self-employed	1 (3.1)	2 (6.3)	
Unemployed	16 (50.0)	17 (53.1)	
Marital status			1.00
Single	4 (12.5)	3 (9.4)	
Married	20 (62.5)	21 (65.6)	
Divorced	8 (25.0)	8 (25.0)	
Education			0.63
None	0 (0.0)	1 (3.1)	
Primary school	8 (25.0)	7 (21.9)	
High school	6 (18.8)	7 (21.9)	
Diploma	3 (9.4)	2 (6.3)	
Bachelor	12 (37.5)	8 (25.0)	
Master or higher	3 (9.4)	7 (21.9)	
Health insurance			0.14
Civil servant medical benefit scheme	18 (56.3)	21 (65.6)	
State enterprise	7 (21.9)	2 (6.3)	
Universal coverage	0 (0.0)	1 (3.1)	
Social security	0 (0.0)	0 (0.0)	
Cash	7 (21.9)	8 (25)	
Income (Baht)			0.54
None	6 (18.8)	2 (6.3)	
<10,000	11 (34.4)	12 (37.5)	
10,000 to 50,000	12 (37.5)	14 (43.7)	
>50,000	3 (9.4)	4 (12.5)	
Diagnosis			0.45
No diabetes retinopathy	25 (78.1)	19 (59.4)	
Mild NPDR	3 (9.4)	7 (21.9)	
Moderate NPDR	3 (9.4)	4 (12.5)	
Severe NPDR	1 (3.1)	2 (6.3)	

UWF=ultrawide-field fundus photography; NPDR: non-proliferative diabetes retinopathy; IQR=interquartile range

* p-value: Fisher's exact test

Table 2. Cost analysis of diabetes retinopathy screening methods

	Pharmacological pupil dilatation	Non-mydriatic UWF
A. Direct medical costs (Baht)		
Visual acuity test	38.40	38.40
Slit-lamp examination	115.20	115.20
Pupil dilatation procedure	64.00	N/A
Mydriatic drug	6.40	N/A
Fundus photography	N/A	153.60
Total	224.00	307.20
B. Direct non-medical costs (Baht); mean±SD		
Transportation cost	178±126	252±342
Meal cost	144±98	156±98
Accommodation cost	0	0
Informal care cost		
• GNI	1,671±1,570	1,100±1,283
• Income	150±215	96±173
Total direct non-medical costs		
• GNI	1,992±1,656	1,507±1,408
• Income	472±332	503±416
C. Indirect costs (Baht); mean±SD		
Total indirect cost		
• GNI	159±48	97±30
• Income	239±312	190±362
D. Total costs (Baht); mean±SD		
Total cost		
• GNI	2375±1,665	1,916±1,419
• Income	934±351	1,006±470

UWF=ultrawide-field fundus photography; GNI=Gross National Income; SD=standard deviation

Table 3. Cost-effectiveness analysis of pharmacological pupil dilatation versus non-mydriatic ultrawide-field fundus photography

	Total cost (Baht)	Effectiveness (case detected)	ICER (Baht/ case detected)
Hospital perspective			
Pharmacological pupil dilatation	224	100	
Non-mydriatic UWF	307	94	–13.87
Societal perspective			
GNI			
• Pharmacological pupil dilatation	2,375	100	
• Non-mydriatic UWF	1,916.45	94	76.46
Income			
• Pharmacological pupil dilatation	934	100	
• Non-mydriatic UWF	1005.73	94	–11.88

ICER=incremental cost-effectiveness ratio; UWF=ultrawide-field fundus photography; GNI=Gross National Income

Cost analysis

DMC, DNMC, indirect costs, and total costs of the DR screening program are presented in Table 2. For DMC, the patients in both groups received visual acuity test and slit-lamp examination that costed 38.40 and 115.20 Baht, respectively. Additional costs for those patients in the pharmacological pupil dilatation group were the pupil dilatation procedure and mydriatic drug, which costed 64.00 and 6.40 Baht, respectively. On the other hand, in the UWF group, the additional expense was fundus photography, which costed 153.60 Baht. The total DMC for the pharmacological pupil dilatation and the UWF groups were 224.00 and 307.20 Baht, respectively. For DNMC, there was no accommodation cost for either group. The total DNMC based on the GNI per capita were 1,992 and 1,507 Baht for the pharmacological pupil dilatation and the UWF groups, respectively. In addition, the total DNMC based on the income provided by the patients' caregivers were 472 and 503 Baht for the pharmacological pupil dilatation and the UWF groups, respectively. Meanwhile, the indirect costs based on the GNI per capita were 159 and 97 Baht for the pharmacological pupil dilatation and the UWF groups, respectively. The indirect costs based on the income provided by either patients or their caregivers were 239 and 190 Baht for the pharmacological pupil dilatation and the UWF groups, respectively. Finally, the total costs included DMC, DNMC, and indirect costs were also calculated. Based on the GNI per capita and the income, the authors found that the total costs were 2,375 versus 934 Baht and 1,916 versus 1,006 Baht for the pharmacological pupil dilatation and the UWF groups, respectively.

Cost-effectiveness analysis

The ICERs of UWF compared with those of pharmacological pupil dilatation in DR screening program are presented in Table 3. UWF had a sensitivity of 94% with specificity of 100%[11]. Cost-effectiveness analysis from hospital perspective showed the ICER of UWF to be –13.87 Baht per case detected due to higher DMC and lower sensitivity when compared with pharmacological pupil dilatation. The ICER of UWF from societal perspective using the GNI per capita was 76.46 Baht per case detected due to lower total costs compared with pharmacological pupil dilatation. On the other hand, the ICER of UWF from societal perspective using the income was –11.88 Baht per case detected due to higher total costs and lower sensitivity compared with pharmacologically pupil dilatation.

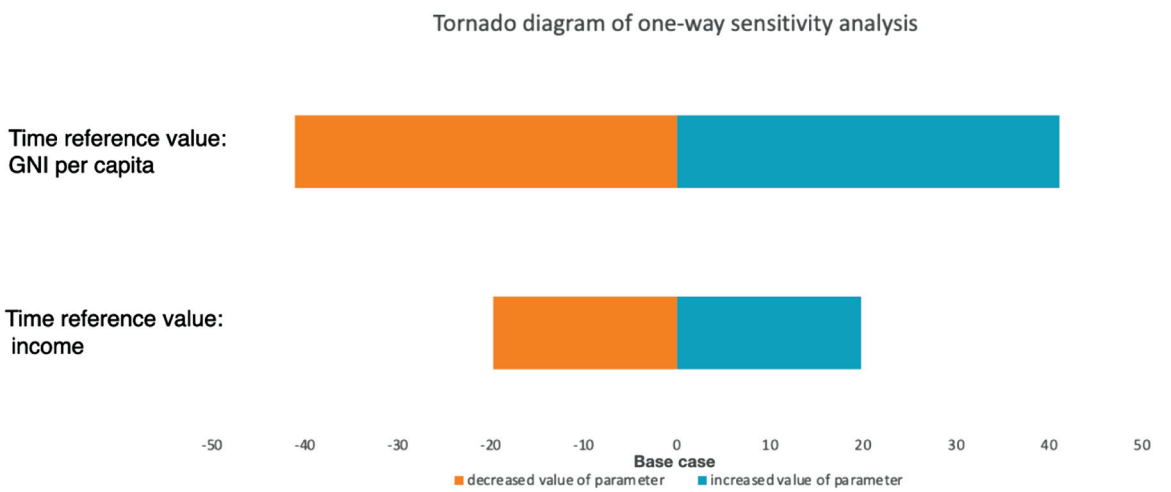

Figure 1. Tornado diagram of one-way sensitivity analysis.

One-way sensitivity analysis

One-way sensitivity analysis was performed by varying perspective such as hospital and societal, and time reference values using GNI per capita and income. Table 3 reports the results from one-way sensitivity analysis. The result showed opposite directions of ICERs between the hospital and societal perspective, which has a positive value for the societal perspective and a negative ICER from the hospital perspective. Similar to the alternation of time reference value, there were positive ICER when calculated with the GNI per capita but negative ICER when calculated with the income. The ICER from societal perspective using GNI per capita as a time reference value was the most sensitive variable as shown in Figure 1.

Discussion

The UWF screening has several advantages over the conventional procedure of pharmacological pupil dilatation as abovementioned. The results from the cost-effectiveness analysis at Chulabhorn Hospital showed alternated values of the ICER for UWF based on which values were taken into consideration. In the hospital perspective, the ICER was negative due to higher cost of the equipment and subsequent higher cost for UWF screening, while the sensitivity for the detection was 94% referencing a previous study[11]. In the meantime, for the societal perspective, the ICER was also negative when taking the patients and their caregivers' incomes into consideration. This was possibly due to the UWF group had higher DMC than the other group. However, when taking the GNI into account, the ICER value became positive. This was potentially due to UWF provided shorter screening time and bypassing post-screening blurred vision[13]. The patients and their caregivers spent less time on screening day and the patients could perform daily activity afterwards. For these reasons, UWF was superior to pharmacological pupil dilatation from the societal perspective, under threshold of willingness to pay, which was 1.2 times of GNI per capita in 2018 value or 193,000 Baht[14].

Based on these results, it was inconclusive whether UWF should replace pharmacological pupil dilatation for DR screening. The ICER based on the income, after the one-way sensitivity analysis, was negative as the patients at Chulabhorn Hospital are more likely to have higher income than the general population in Thailand since the hospital is located in the metropolitan area of Bangkok. However, for a broader perspective, UWF should be used based on the GNI referenced calculation, which the ICER was shown to be positive[12]. The results are in accordance with previous studies that demonstrated that non-mydriatic fundus photography is a cost-effective approach for DR screening[8-10]. Thus, non-mydriatic fundus photography has been suggested as an effective approach in DR screening where it is feasible[15].

Most of the studies, related to non-mydriatic fundus photography, up until present have demonstrated the points of single-field non-mydriatic fundus photography, which has a sensitivity for DR detection of approximately 68%[16]. The UWF, which had been used in the present study was shown to have a 94% sensitivity with 100% specificity[11]. However, the referenced value has now been reported over a

decade ago. Therefore, the 94% sensitivity might have been improved, which could affect the analysis results of the present study.

Although the result of the present study could implicate the benefits of UWF for the general public, the study is simply based on the population at Chulabhorn Hospital, which a further larger study should be conducted in multicenter to represent the national population for setting up a new practical guideline. Based on the current results, using GNI per capita in the societal perspective, it can be speculated that UWF is a viable option for DR screening.

Conclusion

UWF for DR screening have greater cost-effectiveness compared with pharmacological pupil dilatation in patients with type 2 diabetes mellitus. For hospital perspective, the lower cost-effectiveness was largely due to high investment cost of UWF instrument. However, the results of the present study were based on the information from urban population. Multicenter study is required for national representation.

What is already known on this topic?

UWF imaging for DR screening was shown to have a sensitivity of 94% and specificity of up to 100%[11]. Although UWF presented comparable outcomes to pharmacological pupil dilatation, the major limitation of using this machine is the instrument cost. There was a limited number of studies focusing on cost-effectiveness of UWF in routine DR screening.

What this study adds?

This study reported the cost-effectiveness between UWF and pharmacological pupil dilatation in terms of hospital and societal perspectives. The use of UWF has a better cost-effectiveness in societal perspective, which means that UWF could be a viable option for DR screening in national setting.

Acknowledgement

Foundation: Chulabhorn Royal Academy (project number RAA2561/015).

The authors would like to thank Pannapa Sangmala at the Department of Research Innovation and International Relations, for generous support and insightful advice on the study. The authors are also grateful for Waraporn Krongthong for her kind assistance in conducting the statistical analysis.

Conflicts of interest

The authors declare no conflict of interest.

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