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Original Research

Prevalence, severity, and treatment of dry eye disease among patients presenting at community pharmacies in Klang Valley, Malaysia: A cross-sectional study

Huey Ming Pang, Mei Qian Yau, Raja Ahsan Aftab, Renukha Sellappans, Bee Kim Tan

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Abstract

Background: A healthy tear film ensures ocular comfort, high-quality vision, corneal protection from irritants, and facilitates wound healing. Disruption in the tear film causes dry eye disease (DED), a condition affecting millions globally. Untreated DED produces symptoms such as gritty sensations, ocular discomfort, visual impairment, and reduced quality of life. Pharmacological treatment is necessary if symptoms persist after first-line, non-pharmacological therapies. The Asia Dry Eye Society formulated different dry eye classifications based on abnormal components in the surface epithelium and bilayered tear film, to allow pharmacists to implement tear film-oriented therapy. These include artificial tears, diquafosol sodium, ophthalmic ointments, and rebamipide. Community pharmacists facilitate alternative, convenient and increased access to DED treatments. Although DED is widespread in Malaysia, national data on DED identification and management by community pharmacists is limited. **Objectives:** To investigate the prevalence, severity, and treatment options for DED among patients presenting at community pharmacies in Klang Valley, Malaysia. **Methods:** This cross-sectional Ocular Surface Disease Index (OSDI) questionnaire-based study surveyed customers visiting community pharmacies and the retail pharmacists working in these pharmacies in Klang Valley, Malaysia. **Results:** Of the 217 participants included in this study, DED prevalence was found to increase with age (65 years: 80%; <18 years: 25%, p<0.05). Prevalence was highest in Malay participants (49.23%; p<0.05) and significantly higher in those in urban areas (p=0.002). Furthermore, education was associated with DED prevalence in Klang Valley, Malaysia. The most common symptoms reported by DED patients were sensitivity to light (74.39%) and blurry vision (70.73%). Most participants experienced problems with night driving (87.80%) and reading (79.27%). Additionally, 76.83% of patients felt uncomfortable in air-conditioned and low humidity areas, while 73.17% experienced discomfort under windy conditions. The most recommended management options for DED were Systane hydration UD® eye drops and supplements (e.g., fish oil and Eyegard®). **Conclusions:** DED prevalence in Klang Valley, Malaysia, was 37.78%, with the disease being either mild (40.34%), moderate (30.49%) or severe (29.27%). Supplements and artificial tears with high viscosity and pH between 6.6 to 7.8 are frequently recommended to these patients by community pharmacists.

Keywords: Dry eye disease, Ocular Surface Disease Index, community pharmacy, prevalence, severity, treatment

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INTRODUCTION

Tear film disruption leads to dry eye disease (DED), a prevalent condition affecting millions worldwide. A healthy tear film maintains ocular comfort and high-quality vision, protects the cornea from stimulants and/or irritants, and accelerates wound healing.[1] Its three layers comprise an outer lipid layer, an intermediate aqueous layer, and an inner mucin layer, each with unique roles in tear film function. While the glycocalyx-containing mucin layer facilitates the tight attachment of the middle aqueous layer to the corneal and conjunctival epithelia, the lipid layer helps delay lacrimal film evaporation. The aqueous layer,[2] which comprises the majority of the tear film, is composed mainly of water (~98%), and also includes oxygen, electrolytes, immunoglobulin (Ig) A, E, and M. Changes in equilibrium in these layers cause tear film instability, which can trigger dry eyes.

Recent epidemiological investigations revealed a global DED prevalence of 5% to 50% with prevalence rising yearly, indicating that DED is an increasingly serious public health concern. DED is more common in women than men,[3] and ageing has been identified as one key driver of DED prevalence.[4] A Japanese cross-sectional study on DED prevalence and risk factors found it to be more likely among men with low body mass index or

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hypertension, and women with myocardial infarction or angina, who used visual display terminals (VDTs).[5] DED prevalence was also comparatively higher in the Japanese population[6] than similar populations in other countries. In the United States, 6.8% of adults have been diagnosed with DED[3]. In Malaysia, DED is widespread;[7-9] yet research or data on DED prevalence and epidemiological trends in Malaysia remains inadequate. Moreover, the COVID-19 pandemic significantly increased the use of monitors for work and school and may have led to more VDT-related DED.

Without therapy, DED causes bothersome symptoms and signs including gritty sensations, ocular discomfort, visual impairment and lower quality of life (QoL). A 4-step approach for treating DED has been recommended by the 2017 Tear Film and Ocular Surface Society's Dry Eye Workshop II (TFOS DEWS II) Report.[10] Non-pharmacological therapies such as patient education and warm compresses remain the first-line treatment[10] but pharmacological treatment is necessary if symptoms fail to improve. Subsequently, the Asia Dry Eye Society used the abnormalities occurring in the components of the surface epithelium and the bilayered tear film to formulate three different dry eye classifications:[11] aqueous deficient dry eye (ADDE) occurs due to abnormalities in aqueous tears, increased evaporation dry eye (IEDE) results from abnormalities in the lipid layer and/or secretory mucins, and decreased wettability dry eye (DWDE) develops from abnormalities in epithelial cells and membrane-associated mucins. These classifications allow pharmacists to implement tear film-oriented therapy by offering artificial tears, sodium hyaluronate, diquafosol sodium (DQS) or rebamipide for ADDE; or DQS, ophthalmic ointments or warm compresses and lid hygiene products for IEDE; or DQS or rebamipide for DWDE

Community pharmacists play crucial roles in facilitating an alternative, convenient and increased access to treatments for minor ailments like DED, with local pharmacy schemes in some countries now seeking to increase these services.[12] However, there is limited data from Malaysia on DED identification and management by community pharmacists, even within Klang Valley, the country's main administrative and commercial region.

To better understand the contributors to DED in our region (Klang Valley, Malaysia), and understand DED management and treatments offered by community pharmacists, we studied DED prevalence, severity, and treatment among patients presenting to our community pharmacies.

METHODOLOGY

Study Design

Our cross-sectional study used a convenient sampling design of Malaysian Citizens (Taylor's University Human Ethics Committee approval: HEC 2023/038).

Study Population

Patients were recruited from March to June 2023. Included participants were either patients with a diagnosis of DED according to Ocular Surface Disease Index (OSDI) tests[13-15] who presented at community pharmacies in Klang Valley, or retail pharmacists working at community pharmacies in Klang Valley. They also had to be able to read the survey in English and Mandarin (see note in Appendix). Excluded participants were those with infections, foreign bodies or extensive ocular surface pathologies; with surgeries within the prior 20 months; not residing in Klang Valley; submitting questionnaires with incomplete responses; unwilling to participate, unable to read the questionnaire in English or Mandarin, or who were repeat patients receiving different treatments for DED. Previous studies of DED prevalence in Malaysia established a study sample size of 14.5%. Using a prevalence-based sample size estimation with a 95% confidence interval, 5% precision, and a 20% dropout rate, our study sample size was calculated to be 191. Before study initiation, study goals were explained and signed consents were obtained. Participation was voluntary and participants could withdraw at any time (before, during or after completing the survey) without negative consequences.

Data Collection

Participants' data was anonymised but allowed for collection of demographic information, and obtained through self-administered questionnaires (in hard copy if needed). Community pharmacists were required to scan quick response codes in the patient's preferred language and state their provided treatment if the patient obtained scored 13 or higher. The three categories in the OSDI questionnaire (general eye complaints, vision quality and environmental triggers) were assessed on a 4-point scale (0, none; 1, some; 2, half; 3, most; and 4, all of the time), and OSDI total score was estimated using the following formula: OSDI = [(sum of the scores for all questions answered × 100)/total number of questions answered] × 4. The total score was calculated on a 100-point scale with higher scores indicating greater distress (0 to 12, normal; 13 to 22, mild DED; 23 to 32, moderate DED; >33, severe DED). Participants received an email notification after submitting the questionnaire and were instructed by pharmacists to calculate severity scores. Pharmacists then suggested treatments based on severity, and recorded treatment recommendations for participants scoring 13 or higher. The Chinese version of the questionnaire, C-OSDI[16] which previously underwent translation and validation from the original English version of OSDI,[17] was adapted for this study. Questionnaire validation to account for cultural differences produced Cronbach's alpha values of 0.874 for the English OSDI survey and 0.827 for the Mandarin version (Figure A1 and A2). The community pharmacists received MYR10 incentive for each patient recruited.

Data Analysis

The relationship between each questionnaire component (e.g., age, gender, contact lens wear) and DED prevalence and severity was analysed by descriptive statistics (SPSS version 27; IBM, Armonk, New York, USA). Significance ($p<0.05$) was calculated using Chi-square (χ^2) and Fisher's exact tests. Effect size was analysed using Cohen's d.

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RESULTS

Demographics

Of 230 patients approached (Table 1), 13 were excluded for living outside Klang Valley or for having ocular surgery within the prior 20 months. Participants' mean age was 39.5 years (27.6% were 25-34 years old while 2.3% were over 65 years), 53.9% were female, 48.8% were ethnically Chinese, 14.3% lived in Kuala Lumpur and 72.8% were not contact lens wearers. The highest education level was a university qualification

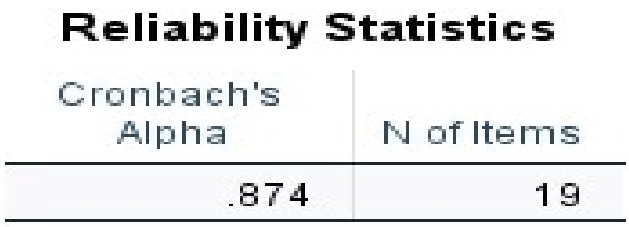

Figure A1. Cronbach's alpha score for English version of OSDI.

Figure A2. Cronbach's alpha score for Mandarin version of OSDI or C-OSDI.

Table 1. Demographics of the study population

		N	%
Age	<18	12	5.50%
	18-24	42	19.40%
	25-34	60	27.60%
	35-44	46	21.20%
	45-54	36	16.60%
	55-64	16	7.40%
	>65	5	2.30%
Gender	Male	100	46.10%
	Female	117	53.90%
Race	Malay	65	30.00%
	Chinese	106	48.80%
	Indian	46	21.20%
Living place	Kuala Lumpur	31	14.30%
	Shah Alam	25	11.50%
	Petaling Jaya	25	11.50%
	Subang Jaya	20	9.20%
	Klang	19	8.80%
	Selayang	18	8.30%
	Ampang Jaya	21	9.70%
	Kajang	18	8.30%
	Sepang	21	9.70%
	Putrajaya	19	8.80%
Highest education level	Primary School	2	0.90%
	Secondary School (SPM)	78	35.90%
	Pre-University	20	9.20%
	Bachelor's degree	111	51.20%
	Master's degree	5	2.30%
	PhD	1	0.50%
Contact lens wearer	No	158	72.80%
	Yes	59	27.20%

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(bachelor's degree; 51.2%), followed by a secondary school (35.9%) qualification

DED Prevalence

The prevalence of DED in Klang Valley was 37.78% (82/217), DED was mild in 15.2%, moderate in 11.5%, and severe in 11.1%. Education contributed to DED occurrence (Table 2), with the highest prevalence among pre-university students (65%), followed by individuals with a master's degree (60%; p<0.05). A statistically significant difference in DED prevalence was observed in 80% of those aged 65 years and older, 62.5% of those aged 55-64 years and 45.24% of those aged 18-24 (p<0.05) (Table 2). DED prevalence was also highest among ethnic Malays (49.23%), followed by ethnic Chinese (39.62%), and 17.39% in ethnic Indians (p<0.05). A strong and statistically significant difference was observed between location of residence and DED prevalence; 73.68% of those with DED lived in Putrajaya, 60.0% lived in Subang Jaya and 45.16% lived in Kuala Lumpur (p=0.002), whereas Sepang had the lowest rate of DED (23.81%) (**Table A1)**.

DED Severity

DED was either mild (40.24%), moderate (30.49%) or severe (29.27%) (Table A2). The most frequently reported symptoms were sensitivity to light (74.39%) and blurred vision (70.73%), with eye pain in 58.54% of patients. Driving at night was difficult for 87.80% of patients, while 79.27% experienced difficulties with reading. Environmental factors that triggered DED (Table

Table 2. Factors linked with the severity of DED.

		Severity				Total, n=217	p-value
		Normal, n=135	Mild, n=33	Moderate, n=25	Severe, n=24		
Age	<18	9	1	1	1	12	0.044
	18-24	23	8	5	6	42	
	25-34	34	8	8	10	60	
	35-44	37	6	3	0	46	
	45-54	25	6	2	3	36	
	55-64	6	4	4	2	16	
	>65	1	0	2	2	5	
Gender	Male	69	14	11	6	100	0.117
	Female	66	19	14	18	117	
Race	Malay	33	10	10	12	65	0.010
	Chinese	64	18	15	9	106	
	Indian	38	5	0	3	46	
Living place	Kuala Lumpur	17	7	6	1	31	0.002
	Shah Alam	18	1	0	6	25	
	Petaling Jaya	17	1	4	3	25	
	Subang Jaya	8	9	1	2	20	
	Klang	15	2	1	1	19	
	Selayang	13	2	2	1	18	
	Ampang Jaya	14	3	2	2	21	
	Kajang	12	4	2	0	18	
	Sepang	16	0	3	2	21	
	Putrajaya	5	4	4	6	19	
Highest education level	Primary School	1	0	1	0	2	0.023
	Secondary School (SPM)	48	11	9	10	78	
	Pre-University	7	3	3	7	20	
	Bachelor's degree	76	19	11	5	111	
	Master's degree	2	0	1	2	5	
	PhD	1	0	0	0	1	
Contact lens wearer	No	103	22	19	14	158	0.248
	Yes	32	11	6	10	59	

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Table A1. Demographic characteristics in both groups.

		With DED n=82	Without DED n=135	Total n=217
Age	<18	3	9	12
	18-24	19	23	42
	25-34	26	34	60
	35-44	9	37	46
	45-54	11	25	36
	55-64	10	6	16
	>65	4	1	5
Gender	Male	31	69	100
	Female	51	66	117
Race	Malay	32	33	65
	Chinese	42	64	106
	Indian	8	38	46
Living place	Kuala Lumpur	14	17	31
	Shah Alam	7	18	25
	Petaling Jaya	8	17	25
	Subang Jaya	12	8	20
	Klang	4	15	19
	Selayang	5	13	18
	Ampang Jaya	7	14	21
	Kajang	6	12	18
	Sepang	5	16	21
	Putrajaya	14	5	19
Highest education level	Primary School	1	1	2
	Secondary School (SPM)	30	48	78
	Pre-University	13	7	20
	Bachelor's degree	35	76	111
	Master's degree	3	2	5
	PhD	0	1	1
Contact lens wearer	No	55	103	158
	Yes	27	32	59

3) included air-conditioning and low humidity (76.83%), and windy conditions (73.17%).

DED Treatment

Community pharmacists in Klang Valley most frequently recommended Systane Hydration UD® (30.3%) to treat mild DED (Figures 1), supplements (Eye Gard®, 40.0%) to treat moderate DED (Figure 2), and fish oil (33.3%) to treat severe DED (Figure 3Table A3-A4).

DISCUSSION

We identified ageing as a primary contributor to DED occurrence in Klang Valley, Malaysia, with DED significantly affected by education,[18, 19] but not by gender or contact lens use ($p>0.05$). Compared to older studies, we found a higher DED prevalence in Klang Valley (15%)[20] and the highest prevalence among Malay participants, in agreement with a more recent cross-sectional study showing the highest prevalence among Malays, followed by Chinese and Indians.[21] DED rates were higher in urban (Putrajaya, Subang Jaya and Kuala Lumpur) populations than in suburban or rural (Sepang) populations, likely due to air pollution or poor air quality in urban areas exacerbating DED.[22, 23] In the urbanised Klang Valley region, the main air pollutant, particulate matter 2.5 ($PM_{2.5}$), increases tear secretion while reducing conjunctival goblet cell density. Additionally, high ozone concentrations in polluted air reduce basal tear secretion.[24, 25] Consequently, residents in these areas have a higher risk of ocular discomfort. Air pollution is the result of economic growth and urbanisation, however our results show that it significantly threatens public health by exacerbating DED. Although the Malaysia government

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Table 3. Environmental factors trigger the DED.

			Severity		
Questions	**Factors**	**Frequency**	**Mild**	**Moderate**	**Severe**
Have you experienced any of the following during the last week	Eyes that are sensitive to light	None of the time	10	9	2
		Some of the time	18	13	8
		Half of the time	2	2	5
		Most of the time	3	1	8
		All of the time	0	0	1
	Eyes that feel gritty	None of the time	17	8	4
		Some of the time	14	10	8
		Half of the time	2	6	9
		Most of the time	0	1	3
		All of the time	0	0	0
	Painful or sore eyes	None of the time	22	9	3
		Some of the time	10	14	10
		Half of the time	1	1	8
		Most of the time	0	1	3
		All of the time	0	0	0
	Blurred vison	None of the time	19	4	1
		Some of the time	11	17	5
		Half of the time	2	3	7
		Most of the time	0	1	8
		All of the time	1	0	3
	Poor vision	None of the time	18	6	2
		Some of the time	13	16	5
		Half of the time	1	1	5
		Most of the time	1	1	8
		All of the time	0	1	4
Have problems with your eyes limited you in performing any of the following during the last week	Reading	None of the time	11	5	0
		Some of the time	21	15	11
		Half of the time	1	3	7
		Most of the time	0	2	4
		All of the time	0	0	1
		N/A	0	0	1
	Driving at night	None of the time	7	2	0
		Some of the time	24	13	6
		Half of the time	2	8	5
		Most of the time	0	1	9
		All of the time	0	0	4
		N/A	0	1	0
	Working with a computer or bank machine (ATM)	None of the time	20	6	1
		Some of the time	12	10	7
		Half of the time	1	6	4
		Most of the time	0	1	7
		All of the time	0	1	3
		N/A	0	1	2

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	Watching TV	None of the time	16	8	2
		Some of the time	12	10	7
		Half of the time	2	4	5
		Most of the time	2	1	9
		All of the time	0	2	1
		N/A	1	0	0
Have your eyes felt uncomfortable in any of the following situations during the last week	Windy conditions	None of the time	14	7	1
		Some of the time	19	14	7
		Half of the time	0	4	9
		Most of the time	0	0	6
		All of the time	0	0	1
		N/A	0	0	0
	Places/areas with low humidity (very dry)	None of the time	12	3	3
		Some of the time	19	15	6
		Half of the time	2	6	5
		Most of the time	0	1	7
		All of the time	0	0	2
		N/A	0	0	1
	Areas that are air-conditioned	None of the time	12	3	3
		Some of the time	19	15	6
		Half of the time	2	6	5
		Most of the time	0	1	7
		All of the time	0	0	2
		N/A	0	0	1

Table A2. Severity of the DED.

		Severity			
		Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	Normal	135	62.2	62.2	62.2
	Mild	33	15.2	15.2	77.4
	Moderate	25	11.5	11.5	88.9
	Severe	24	11.1	11.1	100.0
	Total	217	100.0	100.0	

Table A3. Frequency of the treatments of dry eye disease.

	Treatment	Frequency, N	Percent, %
Valid	Eye Gard	21	25.6
	Fish Oil	15	18.3
	Systane Ultra UD	1	1.2
	Systane Hydration UD	16	19.5
	Systane Complete	1	1.2
	Diquas	1	1.2
	Hialid	14	17.1
	Refresh	10	12.2
	Cationorm	1	1.2

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	Tear Naturale free	2	2.4
	Total	82	100

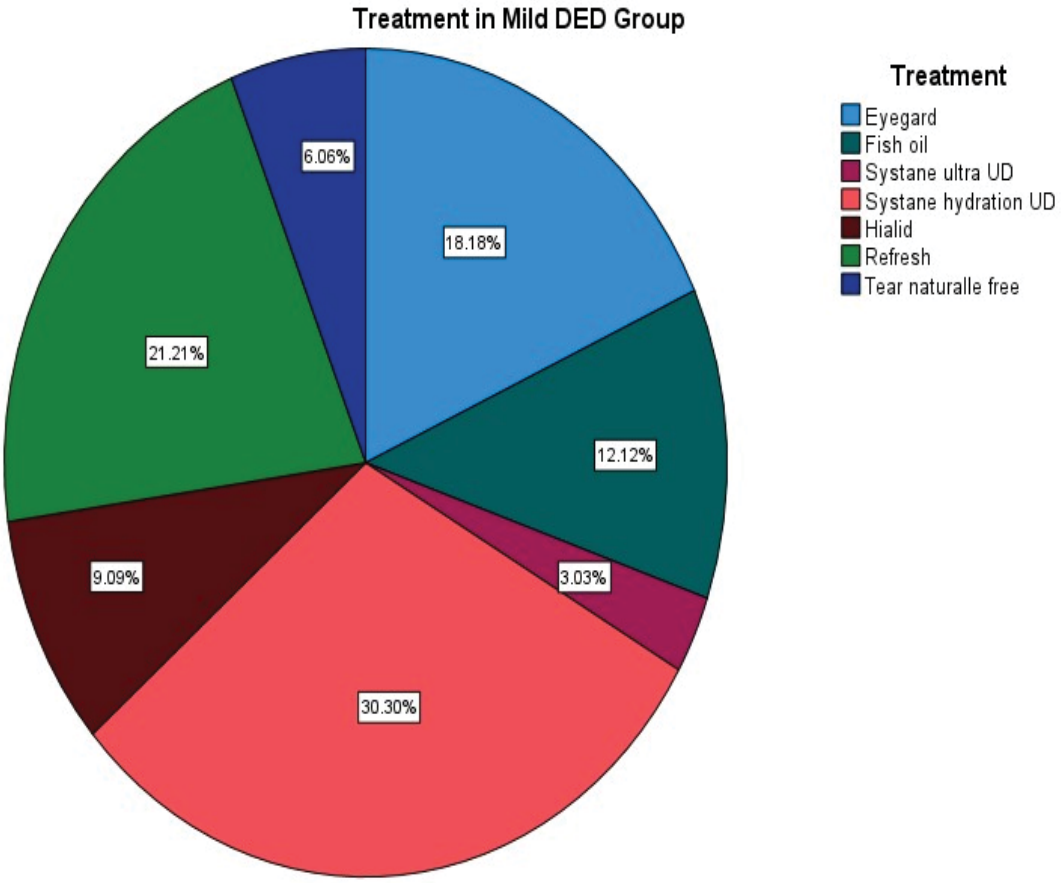

Figure 1. Pie chart representing treatment suggested in mild DED group.

Table A4. Treatments of dry eye disease recommended by the community pharmacists based on different severity**.**

Treatment/ Severity	**Mild**	**Moderate**	**Severe**	**Total**	**p-value**
Eye Gard	6	10	5	21	0.017
Fish Oil	4	3	8	15	
Systane Ultra UD	1	0	0	1	
Systane Hydration UD	10	6	0	16	
Systane Complete	0	0	1	1	
Diquas	0	0	1	1	
Hialid	3	4	7	14	
Refresh	7	2	1	10	
Cationorm	0	0	1	1	
Tear Naturale free	2	0	0	2	

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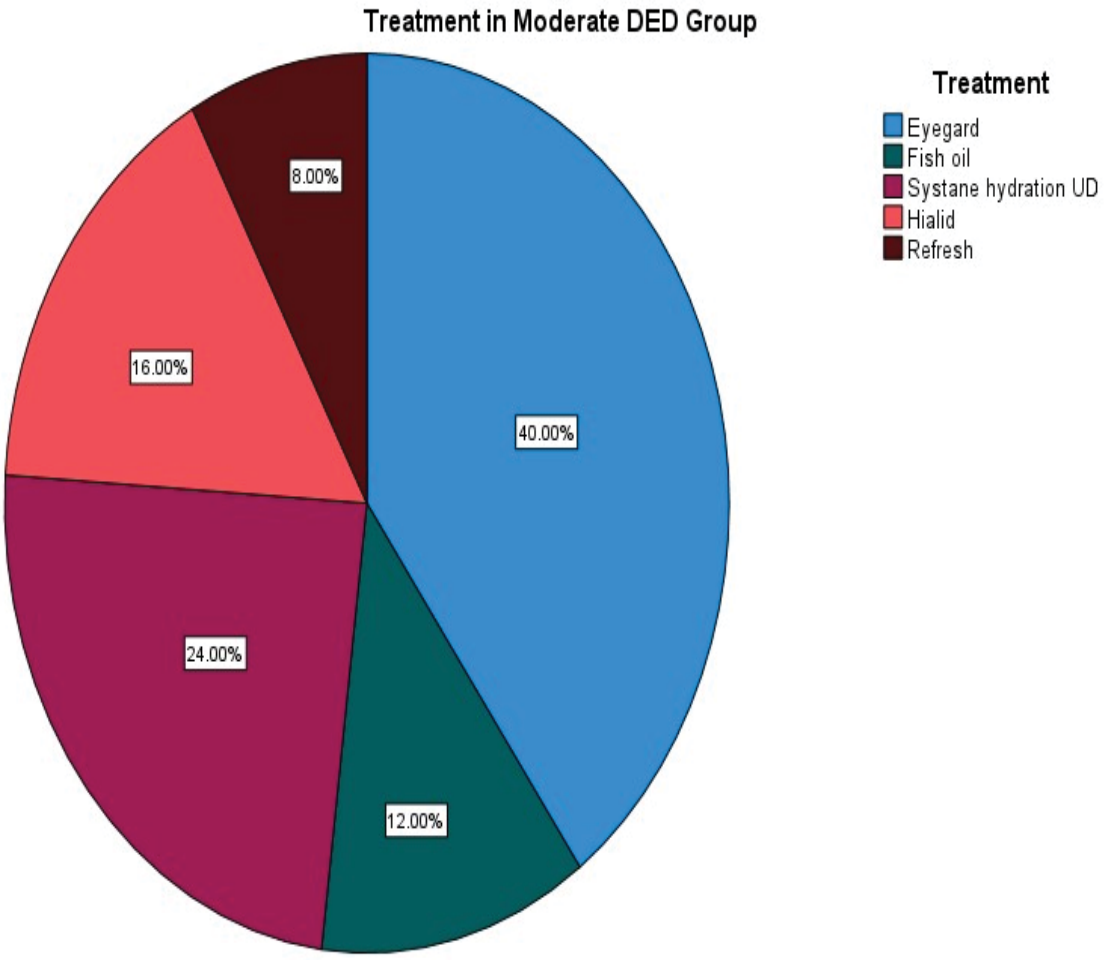

Figure 2. Pie chart representing treatment suggested in moderate DED group.

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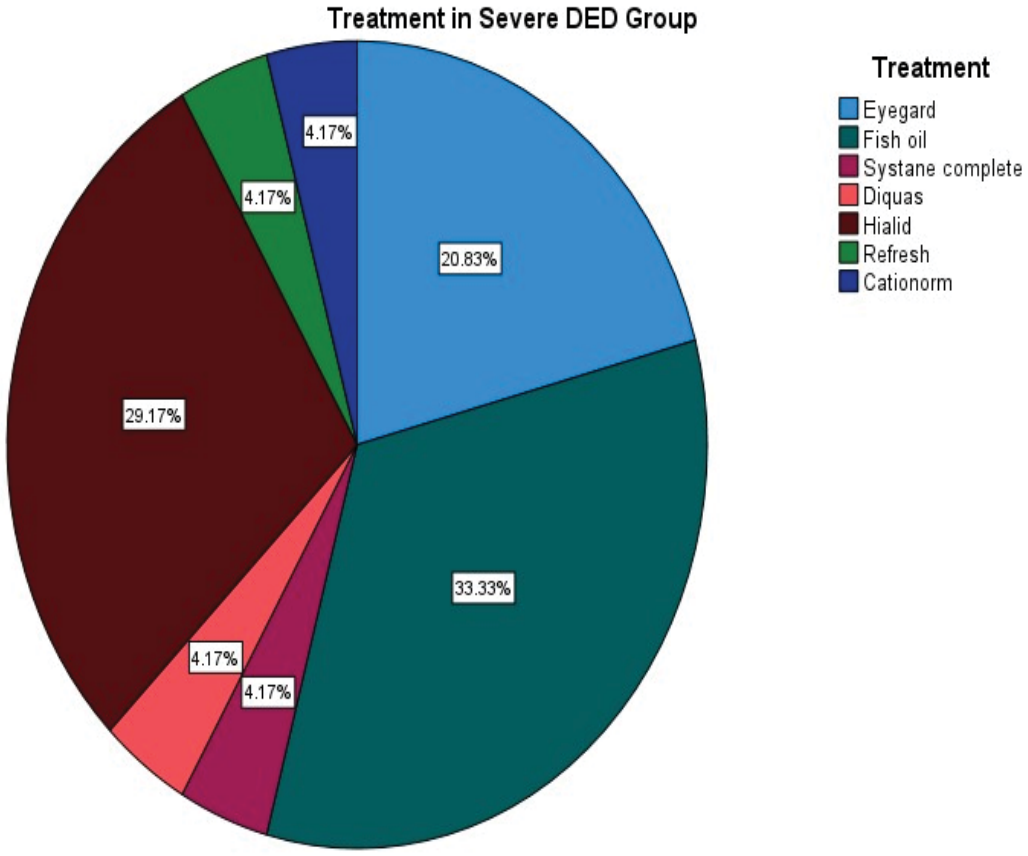

Figure 3. Pie chart representing treatment suggested in severe DED group.

has introduced income tax exception policies to encourage ownerships of electronic vehicle, further low-carbon policies are needed to reduce high health risks due to industrial gases and old motor vehicles in the cities.

Like other studies, our DED patients reported difficulties with driving at night and reading,[26-28] likely as both activities require viewing concentration and less frequent blinking. Thus, DED is a serious issue as it significantly limited daily activities, eventually decreasing quality of life (QoL).[29] We also found that many Klang Valley-residing patients experienced dry eyes when exposed to low humidity and air-conditioned environments, in agreement with studies correlating humidity and DED prevalence.[30-32] For example, the tear film of soft contact lens wearers improved significantly when relative humidity increased from 10% to 45%.[33] Moreover, higher humidity levels were associated with decreased blink frequency and eye closure time, either because of reduced tear production in hot climates or rapid tear evaporation in low humidity and air-conditioned environments.[34]

Artificial tears are the main treatment option for 56.1% of DED patients because they quickly relieve bothersome symptoms including ocular discomfort and eye irritation, are simple to use, cost-effective, and have minimal side effects. Viscosity and pH play vital roles in artificial tears. A pH range of 6.6 to 7.8 prevents ocular discomfort, while more viscous formulations remain on ocular surfaces for longer.[35] Systane Hydration UD® contains 0.1% sodium hyaluronate (HA) and hydroxypropyl-guar (HPG) (HA-HPG). While HA provides sustained hydration and increases the residence time of lubricating drops, the gel-like HPG matrix contains borate ions that prolong the retention of demulcents on damaged ocular surfaces. HPG also decreases inflammatory responses, promotes corneal epithelial healing and stabilises the tear film.[36] HA-HPG is thus an effective DED treatment. Of note, the only formulation with a pH value less than 6.6 was Hialid®.[37] Systane hydration UD was also the most viscous, whereas Cationorm® was the least viscous, and may explain the pharmacists' frequent recommendation of Systane hydration UD®.

EyeGard® is specifically formulated with lutein and bilberry, which have significant eye health benefits.[38] Fish oil has also been shown to improve dry eyes.[39-41] Dietary supplementation with omega-3 fatty acid-containing fish oil, bilberry extract and lutein, may alleviate asthenopia symptoms including eye pain, dry or watery eyes, and difficulties keeping eyes open.[42]

We found that topical cyclosporin and lifitegrast were not recommended by Klang Valley community pharmacists due to their classification as Group B poisons requiring prescriptions. Short-term topical corticosteroids such as prednisolone 1% eye drops are also not usually recommended even though they are approved by the Malaysian National Pharmaceutical Regulatory

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Agency. Eysuvis®, the first DED treatment, is not commercially available in Malaysia.

Given the high prevalence of DED detected in the community pharmacies of Malaysia's Klang Valley, community pharmacists should refer severe cases (which comprised almost one-third of all cases) to ophthalmologists for appropriate diagnosis and management. With convenient access to over-the-counter treatment options for DED, patients with mild-to-moderate symptomatic DED are more likely to be identified when they visit a community pharmacy. Displaying videos at the pharmacy waiting area encourages individuals to conduct DED screening for early detection and referral for further care.

Our current findings on DED epidemiology call for community pharmacists to play active roles in identifying and managing DED in their facilities – a shift from product-based services to patient-centred care practice models. Community pharmacists should expand their roles through patient education and follow-up care as a strategy to optimise outcomes of DED patients who have poor disease control. Moreover, a patient's medical and medication history should be assessed to identify DED risk factors and allow interventions to be tailored to the patients' specific conditions. Capacity building of community pharmacists is crucial not only to provide quality DED care, but also to empower the community to adopt positive lifestyle habits for DED prevention and quality of life improvements.

While our study was conducted in Malaysia, sociodemographic and healthcare financing influence the prevalence, awareness, treatment and control of DED in patient populations, regardless of country. Our findings on DED prevalence, characteristics and treatment may benefit healthcare professionals from countries with similar societal and healthcare settings to Malaysia, and facilitate the formulation of strategies to improve DED care.

Our study was limited by an inadequate participation of elderly patients. As ageing is a major driver of DED prevalence and severity, more older adults should have been enrolled. Information was also lacking on the participants' medications histories and medical illnesses that may contribute to DED, both of which could affect DED prevalence, severity and treatment outcomes. Future studies will need to include a more diverse population and comprehensive data on medications and underlying diseases.

CONCLUSION

To our knowledge, this is the first known study of DED prevalence, severity and treatment among patients visiting Klang Valley community pharmacies, conducted after changes in work and study behaviours caused by COVID-19 pandemic restrictions. A significant increase in screen exposure occurred alongside our detection of a remarkably high prevalence of DED – 37.78% among patients visiting our community pharmacies, many with moderate or severe DED. Supplements and artificial tears with high viscosity and pH between 6.6 to 7.8 are highly recommended to DED patients by the community pharmacists.

AUTHOR CONTRIBUTIONS

Study design: All authors. Data collection: PHM. Data analysis: PHM, YMQ. Manuscript writing: PHM. Manuscript review and approval: BKT, YMQ, RAA, RS.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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