

# Assessment of Direct Costs of Admission Due to Presumed Microbial Keratitis in a Tertiary Referral Hospital in Thailand: A 7-Year Retrospective Study

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**Objective:** To evaluate the direct healthcare cost of admission and examine the effects of cost drivers of treating presumed microbial keratitis (MK) at a tertiary referral hospital.

**Design:** Retrospective study.

**Methods:** A total of 741 patients who presented with MK were included. All information regarding costs was collected, and demographic data were employed for risk factor analysis.

**Results:** The total cost of treating MK over a 7-year period at Rajavithi Hospital was US\$14,514,625.04, while the median cost was US\$10,840.17 per patient (Q1–3, US\$5866.56–24,172.28). The medical professional services were the highest cost category in terms of both total cost of treatment over 7 years and median cost per patient, accounting for US\$6,474,718.43 and US\$5235.20 (Q1–3, US\$2582.79–10,474.24) respectively. In 2020, the total cost of treatment declined, corresponding with fewer hospitalized patients; however, the median cost per patient was the highest of all years, amounting to US\$15,089.90 (Q1–3, US\$8064.17–29102.50), while the median cost per patient from 2014 to 2019 was US\$9969.96 (Q1–3, US\$5177.98–21,942.68). Statistical significance was found in the median cost per patient in 2020 compared to the median cost per patient in 2014–2019 (p-value 0.019). Risk factors associated with the more expensive cost of treatment were longer length of stay (LOS); age more than 60 years old; readmission; diabetes mellitus (DM); hypertension; and heart disease.

**Conclusion:** There were several key factors impacting the direct healthcare costs of severe MK treatment. Medical professional services emerged as the most substantial cost category, while longer hospital stays, older age groups, readmission cases, and comorbidities such as diabetes mellitus, hypertension, and heart disease were all linked to elevated treatment expenses. There were no statistically significant differences in the direct medical expenses during hospitalization associated with treating severe MK, whether the culture results were positive or negative, or regardless of the type of cultured organism utilized.

**Keywords:** corneal ulcer, infectious keratitis, healthcare cost, economic burden

## Introduction

Microbial keratitis (MK) is an infection of the cornea which can lead to visual impairment and corneal blindness. According to a systematic review and meta-analysis on global causes of blindness and distance vision impairment from 1990–2020, it was estimated that approximately 1.3 million people had visual blindness, and 2.9 million suffered from visual impairment due to corneal opacity.<sup>1</sup> It is difficult to uncover epidemiological information specific to MK since most of the data are recorded under the umbrella termed “corneal blindness or corneal opacity” which encompasses a variety of corneal disorders.<sup>1</sup> Corneal infections, trauma, inflammation, degeneration, nutritional deficiencies, dystrophies, and other distinct factors, including onchocerciasis, trachoma, and iatrogenic sources, all contribute to corneal opacification.<sup>2</sup> MK undeniably stands as a notable

contributor to corneal opacification and blindness, exhibiting varying incidence rates among different populations.<sup>2,3</sup> The Asia Cornea Society Infectious Keratitis Study collected data from thirteen study centers and 30 sub-centers in Asia and found that trauma was the commonest risk factor (accounting for 34.7%), and that clinical diagnosis of bacterial infection was slightly more common than that of fungal keratitis (38% vs 32.7%). Among the isolated microorganisms, *Fusarium* was the most prevalent, followed by *Pseudomonas aeruginosa* and *Aspergillus flavus*.<sup>4</sup> While the gold standard for diagnosis of MK is culture from corneal sampling, the median culture positivity rate from clinically diagnosed MK is only 50.3%;<sup>5</sup> therefore, the initial treatment plan is based on presumptive clinical diagnosis, and subsequent treatment is adjusted in accordance with microbiology results. As MK may progress rapidly and be resistant to treatment, therapy should be commenced as a matter of urgency. Topical medication should be started promptly and surgical intervention may be needed to control the infection and prevent visual impairment.<sup>6</sup> Some patients need to be admitted for in-patient treatment in certain scenarios, such as where there is any immediate visual threat; when patients have not responded well to previous treatment at an out-patient department (OPD); when it is advisable to pursue hourly treatment; when follow-up ensuring is required; or when the patient is a child.<sup>7</sup> Generally, the in-patient admission cost varies substantially depending on several factors, such as cause of admission, individual health situation, medications, surgical interventions, investigations, hospital fees and doctors' charges.

The cost of health care is growing constantly. A report from the World Health Organization (WHO) showed that global spending on health rose continually between 2000 and 2018 and reached US\$ 8.3 trillion or 10% of global GDP.<sup>8</sup> With regard to ophthalmology, it has been forecast that the global visual loss burden will increase, with the number of people suffering from blindness or visual impairment expected to rise as the global population grows and ages.<sup>9</sup> To estimate the probable cost of MK treatment in the future, an evaluation of the economic impact of MK treatment is necessary. It has been established that the factors associated significantly with high overall admission costs for MK treatment include length of stay (LOS),<sup>10</sup> old age,<sup>11</sup> and fungal etiology.<sup>12–14</sup>

The purposes of this study were: firstly, to identify the direct healthcare cost of admission and future trends of presumed MK treatment at a tertiary referral hospital in Thailand; and secondly, to examine the effects of cost drivers on direct admission costs.

## Methods

### Study Site and Data Collection

The protocol of this research was reviewed and approved by the ethics committee of Rajavithi Hospital (No. 64100/2564). Rajavithi Hospital is located in the center of Bangkok, Thailand, and it is the largest public hospital under the Ministry of Public Health management and ownership. We have 3 cornea specialists, who are responsible for the assessment of more than 500 referral cornea and external eye disease cases each year. This was a retrospective cross-sectional study using data from medical record audits at Rajavithi Hospital. We identified all patients who were hospitalized with presumed MK between January 1, 2014 and December 31, 2020. We included cases of diagnosis of corneal ulcer (H160), injury of conjunctiva and corneal abrasion without mention of foreign body (S050), and ocular laceration without prolapse or loss of intraocular tissue (S053). All cases were coded according to the International Classification of Diseases, 10th Revision, Clinical Modification Codes (ICD-10-CM). All cases were reviewed. We excluded cases which lacked data required for evaluation, as well as diagnoses without signs of MK. All included cases were confirmed by at least 1 of 3 cornea specialists.

Demographic data from patients' records included gender, age at admission, health insurance coverage, region of residence, nationality, underlying diseases, LOS, number of admissions, initial best corrected visual acuity (BCVA), and treatment according to presumed organism. VA data on first admission date (initial VA) were collected. We classified the distance vision impairment of our study cases into 4 groups according to the international classification of diseases in 2020 as follows.<sup>15</sup> Distance vision impairment: mild - VA  $\geq$  20/60. Moderate - VA  $<$  20/60 and  $\geq$  20/200. Severe - VA  $<$  20/200 and  $\geq$  20/400. Blindness - VA  $<$  20/400. We collected clinical findings at presentation in all cases in this study, including size, depth, and location of the corneal infiltration, and then classified them using a modified version of Jones' grading criteria.<sup>16</sup>

Direct costs of admission are those expenses directly attributed to patient care. To better differentiate the root of treatment expense, we classified costs into 5 categories: hospital services costs; medical professional services costs; investigation costs; operative treatment costs; and non-operative treatment costs. The details of each cost category are described in [Table 1](#).

The Thailand Consumer Price Index (CPI) for medical care was used to convert the cost data to year 2020 values, and the adjusted figure was used for analysis. Using the 2020 exchange rate of 1 US\$ = 35.0 THB, all costs were first calculated in Thai Baht (THB) and then converted to US dollars (US\$).

All methods were conducted in adherence to pertinent guidelines and regulations. The requirement for informed consent from participants was waived by the Institutional Review Board of the Rajavithi Hospital ethics committee due to the retrospective nature of our study. We affirm that the data was anonymized and treated with strict confidentiality. This study was in compliance with the principles outlined in the Declaration of Helsinki.

## Statistical Methods

We performed statistical calculations using SPSS V.26.0 (IBM SPSS Statistics for Windows). Descriptive statistics were used to summarize the demographic characteristics and clinical findings of the study participants. Continuous variables, such as age at admission, LOS, number of admissions, are presented as median and interquartile range (Q1–Q3). Categorical variables, including gender, underlying diseases, treatment based on presumed organism, group of initial visual acuity, age group, and readmission group are presented as frequencies and percentages. For continuous data, distribution was firstly evaluated using skewness and histogram plots. Normal distribution was assumed if skewness was between  $-1.96$  and  $+1.96$ . To compare these variables between two groups, Student's *t*-test and Mann–Whitney test were used for parametric and non-parametric tests respectively. Kruskal–Wallis test was also performed with nonparametric test to determine differences among 3 groups or more. Spearman correlation coefficient was used to determine correlations between age at first visit, LOS and cost of treatment. The interpretation was as follows: weak ( $r=0.00–0.40$ ), moderate ( $r=0.41–0.69$ ), and strong ( $r=0.70–1.00$ ).  $R^2$  was also assessed to determine the strength of the relationship of this correlation, and statistical significance was set at  $p\text{-value}<0.05$ .

## Results

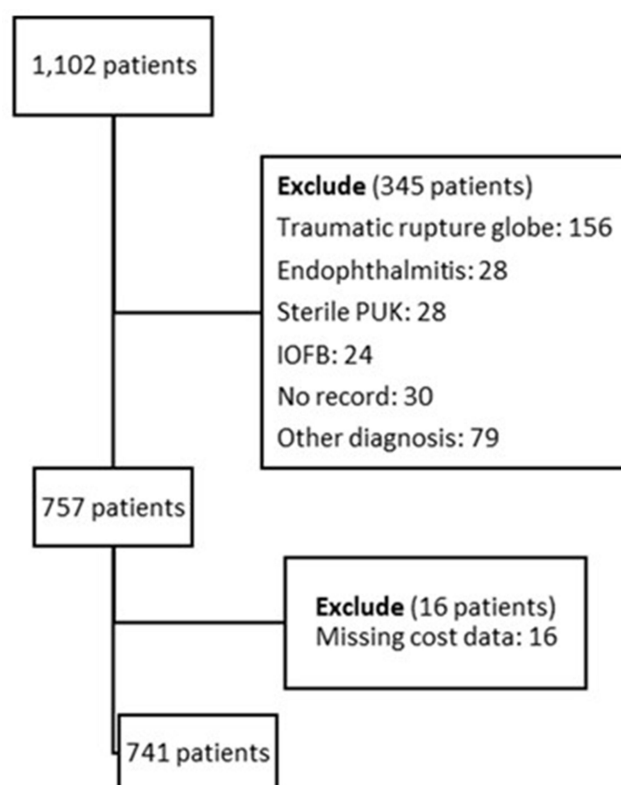
The electronic inpatient records of the 1102 included patients were reviewed. We excluded 345 patients where the main cause of diagnosis was due to other causes, including non-infectious peripheral ulcerative keratitis (PUK), endophthalmitis, traumatic rupture globe and intraocular foreign body (IOFB), as shown [Figure 1](#). The cost data for 16 patients were not completely available, and these cases were therefore excluded, leaving 741 patients with presumed MK with a total of 888 admission visits in the study. The numbers of patients who presented in each year, from 2014 to 2020, were 85, 121, 134, 103, 119, 120, and 59 patients respectively, as shown in [Figure 2](#). All of the cases were classified as severe MK. Severe IK is defined as a diameter greater than 5 mm, a depth greater than 50%, dense infiltrates reaching the deep layers of the corneal stroma, hypopyon, and possibly scleral involvement.<sup>16</sup>

## Costs and Cost Trends

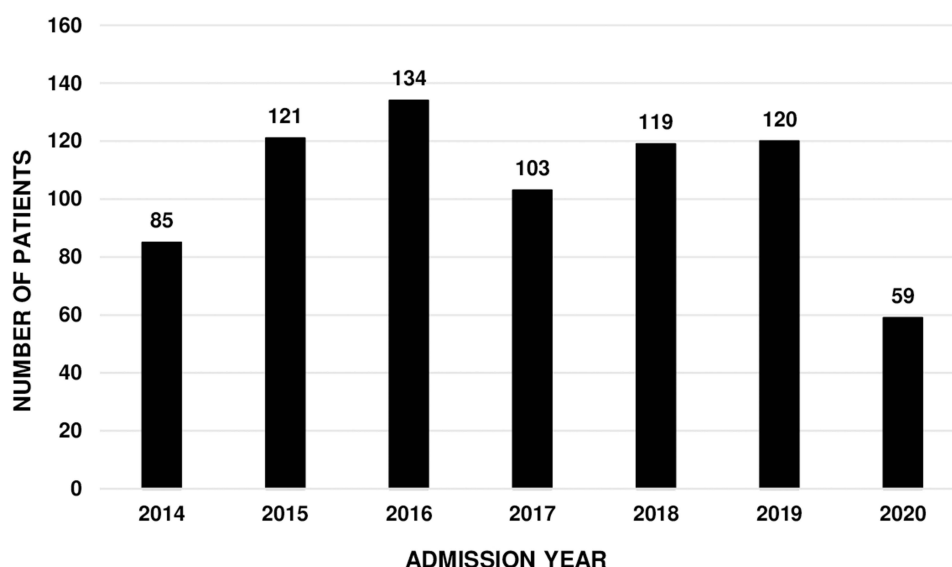
The total cost of treating MK over these 7 years at Rajavithi Hospital was US\$14,514,625.04. The median cost over the 7 years was US\$10,840.17 per patient (Q1–3, US\$5866.56–24,172.28), ranging from US\$864.37 to US\$156,048.35. Details of each

**Table 1** Categories of Direct Cost of Admission for Presumed MK

Category	Details
Hospital services cost	Room/ food services
Medical professional services cost	Doctors/ nurses/ other health care professional cost
Investigation cost	Lab/ imaging / lab/ imaging / other tests
Non-operative treatment cost	Pharmaceuticals/ blood transfusion
Operative treatment cost	Surgical intervention eg. intracameral injection, gluing, corneal biopsy, tarsorrhaphy, penetrating keratoplasty, lamellar keratoplasty, evisceration and enucleation/surgical instruments/anesthesia and related costs



**Figure 1** Flow of the inclusion and exclusion criteria.



**Figure 2** The number of MK patients presenting per year.

sub-category are listed in [Table 2](#) and [Table 3](#). We found that the highest median cost per patient and total cost over 7 years was medical professional services costs, accounting for US\$5235.20 (Q1–3, US\$2582.79–10,474.24) and US\$6,474,718.43 respectively. [Figures 3](#) and [4](#) displays trends of total costs and median costs per patient in each admission year. The total cost showed a slightly decreasing trend. In 2020, we found that total cost of treatment declined, corresponding with fewer hospitalized patients; however, the median cost per patient in 2020 was the highest of all years, amounting to US\$15,089.90 (Q1–3, US\$8064.17–29102.50), while the median cost per patient from 2014 to 2019 was US\$9969.96 (Q1–3, US\$5177.98–

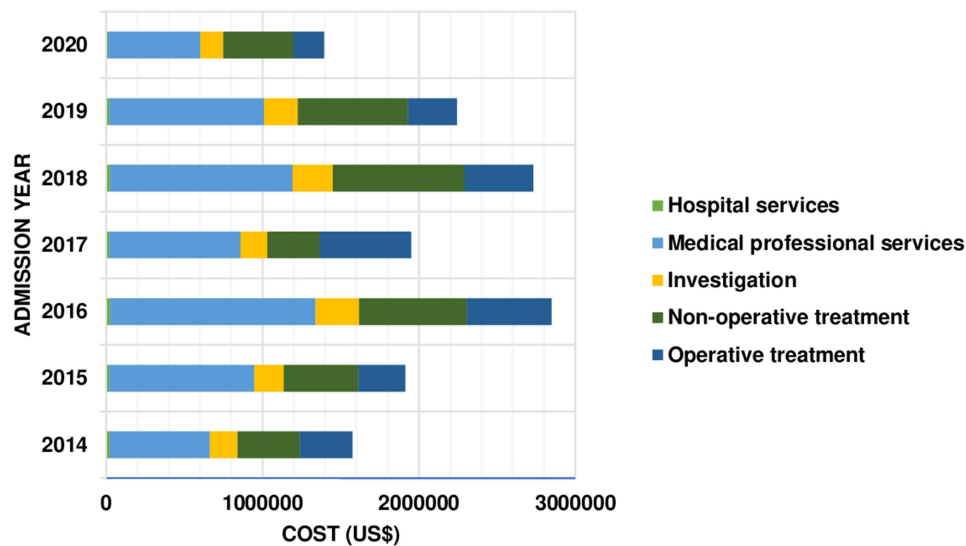
**Table 2** Annual Total Cost in Each Cost Category by Admission Year (2014–2020)

Cost Category	Total Cost Over 7 Years (US\$)	Annual Total Cost (US\$)						
		Admission Year						
		2014	2015	2016	2017	2018	2019	2020
Hospital services	140,851.28	22,071.48	17,786.24	25,196.79	19,428.41	25,174.56	20,216.47	10,977.33
Medical profession services	6,474,718.43	642,144.22	930,912.85	1,313,881.57	839,378.28	1,166,734.74	989,020.88	592,645.90
Investigation	1,436,220.96	177,456.44	187,829.25	278,480.32	171,709.23	257,212.27	217,313.95	146,219.50
Non-operative treatment	2,465,063.58	395,250.43	476,272.82	689,097.23	333,085.20	841,902.57	701,844.57	446,912.20
Operative treatment	4,136,903.02	338,400.47	299,022.50	541,139.79	585,623.20	441,534.45	314,362.16	197,519.00
Total	14,514,625.04	1,553,380.92	1,894,551.92	2,823,077.08	1,930,145.77	2,707,523.08	2,222,602.66	1,383,338.60

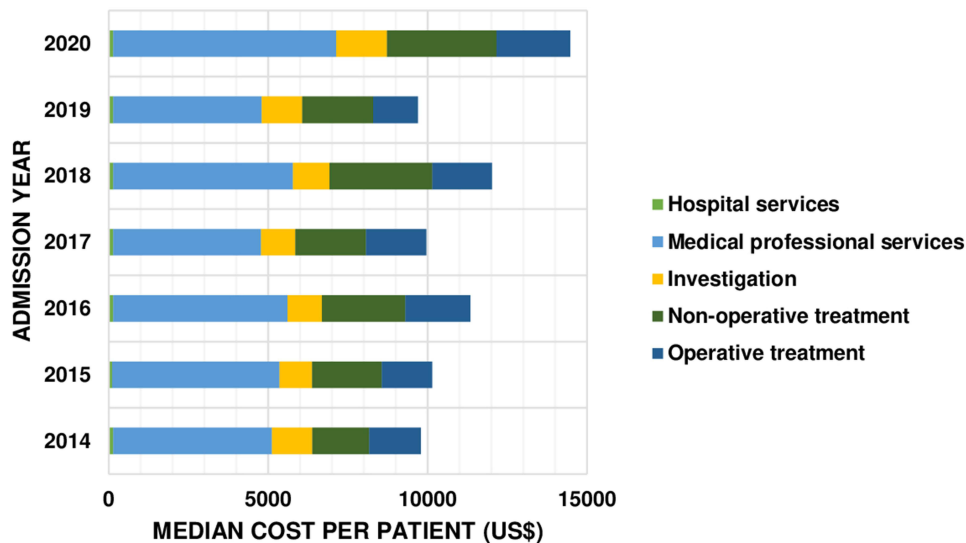
**Table 3** Average Cost per Patient in Each Cost Category by Admission Year (2014–2020)

Cost category	The Average Cost Per Patient in Each Admission Over a 7-Year Period	Cost Per Patient (US\$)							
		Admission Year							
		2014	2015	2016	2017	2018	2019	2020	p-value
<b>Hospital services</b>	137.20 (135.80–140.00)	136.80 (136.80–140.00)	105.00 (105.00–135.00)	138.60 (136.70–140.0)	137.20 (135.80–140.0)	137.20 (135.80–140.0)	135.80 (135.80–136.70)	140.00 (140.00–140.00)	<0.001*
<b>Medical profession services</b>	5235.20 (2582.79–10,474.24)	4986.24 (2301.04–8261.40)	5257.00 (2411.50–10,977.75)	5467.42 (3016.28–11,654.52)	4645.93 (2427.58–7859.84)	5642.35 (3018.40–10,927.55)	4659.63 (2244.09–9811.97)	6989.50 (3202.50–12,643.75)	0.155
<b>Investigation</b>	1174.91 (761.46–2088.97)	1260.28 (635.04–2269.68)	1018.50 (553.87–1835.75)	1077.61 (758.83–1973.31)	1066.73 (686.00–1939.66)	1138.76 (823.20–2140.32)	1273.12 (778.30–2243.24)	1603.00 (943.25–3004.75)	0.143
<b>Non-operative treatment</b>	1836.80 (980.00–3500.00)	1785.28 (824.06–4725.52)	2181.90 (880.07–5593.87)	2615.93 (1189.30–3989.08)	2216.94 (980.00–3385.02)	3234.95 (1101.26–8143.98)	2217.22 (907.90–3377.10)	3430.70 (896.08–10,574.11)	0.040*
<b>Operative treatment</b>	2433.49 (875.84–6270.86)	1618.40 (980.00–3308.20)	1575.00 (735.00–2905.00)	2043.79 (849.36–7171.73)	1888.60 (910.76–4334.63)	1865.85 (1059.36–3807.91)	1406.38 (778.42–6434.81)	2310.00 (1155.00–3815.00)	0.252
<b>Total</b>	<b>10,840.17 (5866.56–24,172.28)</b>	<b>9916.13 (15,414.69–19,556.88)</b>	<b>10,558.45 (4779.77–10,558.45)</b>	<b>11,958.75 (6645.00–25,997.95)</b>	<b>9570.90 (5731.03–18,598.57)</b>	<b>11,654.79 (7114.59–26,416.98)</b>	<b>9761.59 (4984.70–24,699.01)</b>	<b>15,089.90 (8064.17–29,102.50)</b>	<b>0.019*</b>

**Notes:** Values are presented in US\$ as median (Q1–Q3). p-values were calculated using Kruskal Wallis test among admission year. \*Significant p-value <0.05.



**Figure 3** Trends of total cost of treatment in each admission year.



**Figure 4** Trends of median cost per patient in each admission year.

21,942.68). Statistically significant differences were observed in the median total cost per patient in 2020 when compared to the median total cost per patient in 2014–2019. Additionally, statistically significant differences were found in non-operative treatment and hospital services costs per patient in 2020 compared to the median total cost per patient in 2014–2019, while no significant differences were observed in other cost categories.

## Gender

Of the 741 patients, 462 (62.3%) were male and 279 (37.7%) were female. The median treatment costs per patient showed no statistically significant difference between males and females (US\$11,713.92 (Q1–3, US\$6107.50–24,687.30) vs US\$9030.89 (Q1–3, US\$5473.66–25,502.42) respectively,  $p$ -value=0.225) (Table 4).

## Age

The mean age of the patients in this study was 52.4 (range, 7–95) years old. We explored the correlation between age and cost and found a weak but significant correlation between patient age and cost in the study ( $R^2=0.0034$ ,  $p<0.001$ ). Pearson's correlation coefficient revealed a small, but significant, positive relationship. ( $r=0.34$ ,  $p<0.001$ ).

**Table 4** Patient Demographics, Readmission, Underlying Diseases, and Treatment Costs

Demographic Factor	Group	Number of Patients (%)	Median Cost Per Patient (US\$)	IQR (US\$)	p-value
Gender	Male	462 (62.3)	11,713.92	6107.50–24,687.30	0.225 <sup>a</sup>
	Female	279 (37.7)	9030.89	5473.66–\$25,502.42	
Age group (years)	<30	84 (11.4)	4294.22	3881.52–\$8013.55	<0.001 <sup>a,*</sup>
	30–60	384 (51.8)	11,713.71	5567.38– \$24,434.15	
	>60	273 (36.8)	13,123.24	8121.85– \$29,699.60	
Readmission	Single admission	626 (87.6)	8692.56	5229.29–19,305.94	<0.001 <sup>a,*</sup>
	Readmission	115 (12.4)	33,019.89	18,834.73–46,095.59	
<b>Underlying disease</b>					
Hypertension	Yes	185 (24.9)	13,356.24	8453.24–29,157.31	<0.001 <sup>a,*</sup>
	No	556 (75.1)	9948.74	5229.01–23,247.28	
Diabetes mellitus	Yes	103 (13.9)	13,831.37	1961.94–28,067.89	0.007 <sup>a,*</sup>
	No	638 (86.1)	10,499.32	5491.74–24,010.05	
Heart disease	Yes	38 (5.12)	19,509.84	13,129.86–44,021.20	<0.001 <sup>a,*</sup>
	No	703 (94.8)	10,478.58	5586.042–23,765.78	
HIV infection	Yes	30 (4.04)	13,537.72	6718.85–30,287.58	0.491 <sup>a</sup>
	No	711 (95.96)	10,752.84	5829.36–24,103.88	
Kidney disease	Yes	15 (2.02)	17,902.36	11,982.93–28,041.13	0.199 <sup>a</sup>
	No	726 (97.98)	10,738.28	5734.98–24,110.35	
Initial BCVA	≥20/60	27	8323.07	5972.26–13,017.50	0.355 <sup>b</sup>
	20/60–≥20/200	65	9510.56	4370.72–15,310.67	
	20/200–≥20/400	27	10,644.91	7859.83–17,300.46	
	<20/400	622	10,977.80	6678.08–23,774.25	

**Notes:** <sup>a</sup>p-values were calculated using Mann–Whitney U-Test. <sup>b</sup>p-values were calculated using Kruskal Wallis test. \*Significant p-value <0.05.

**Abbreviations:** IQR, Interquartile Range; BCVA, best corrected visual acuity; HIV, Human Immunodeficiency virus.

## Age Group

To better highlight the cost of MK treatment, we stratified patients into 3 groups according to their age at MK diagnosis as group 1 (<30 years old), group 2 (30 to 60 years old), group 3 (>60 years old or more). There were 84 (11.4%), 384 (51.8%) and 273 (36.8%) in each group, respectively, and their median costs per patient were US\$4294.22 (Q1–3, US\$3881.52–8013.55), US\$11,713.71 (Q1–3, US\$5567.38–24,434.15) and US\$13,123.24 (Q1–3, US\$8121.85–29,699.60) respectively. All differences among these groups were statistically significant p-value <0.001 via Kruskal Wallis test (Table 4).

## Readmission

There were 888 admission visits by the 741 patients in this study, ranging from 1 to 6 admissions per patient. Patients were grouped into 2 categories: single admission (626 patients, 87.6%), and readmission (115 patients, 12.4%). In the readmission category, 92, 17, 4, 1, and 1 patients had 2, 3, 4, 5, and 6 hospital readmission visits, respectively.



The total cost per patient was US\$8692.56 (Q1–3, US\$5229.29–19,305.94) in single admission group and US\$33,019.89 (Q1–3, US\$18,834.73–46,095.59) in readmission group, statistically significant difference with  $p<0.001$ . Patients in the readmission group tended to stay longer than those in the single admission group, at 34 days (Q1–3, 21–48 days) and 15 days (Q1–3, 7–23 days,  $p<0.001$ ) respectively (Table 4).

## Underlying Disease

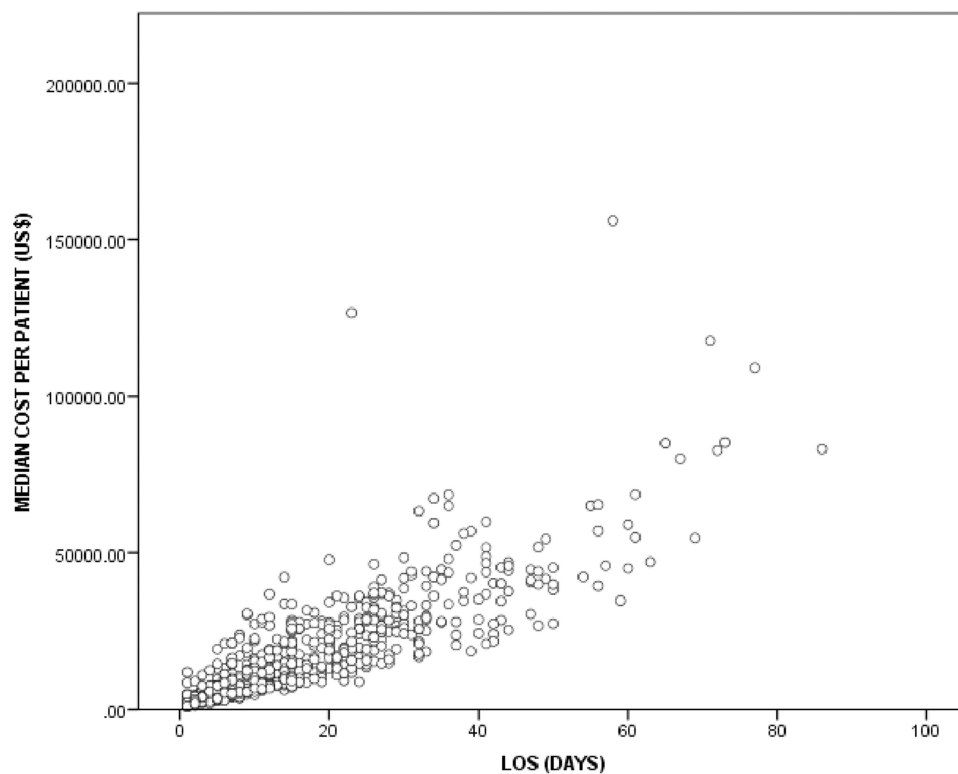
A total of 297 (40.1%) patients had prior underlying diseases. Among these 297 patients, hypertension was the most common underlying disease, accounting for 185 patients followed by diabetes mellitus (DM) 103 patients, heart disease 38 patients, HIV 30 patients and kidney disease 15 patients. The cost of treating MK patients with hypertension, DM, and heart disease were higher than therapy for those without these diseases with statistically significance difference  $p<0.001$ ,  $p=0.007$ , and  $p<0.001$ , respectively, while the other two underlying conditions showed no statistically significant differences, as shown in Table 4.

## Initial Best Corrected Visual Acuity

A total of 620 patients (83.7%) initially presented with blindness. Of the rest, 33 (4.5%), 53 (7.2%) and 32 (4.3%) had severe visual impairment, moderate visual impairment, and normal to mild visual impairment, respectively. Patients with blindness incurred the highest cost of all groups. Statistical significance was found when comparing moderate visual impairment vs severe visual loss ( $p=0.04$ ) and moderate visual impairment vs blindness ( $p<0.001$ ), as shown in Table 3.

## Length of Stay

The median LOS was 12 days, ranging from 1 to 86 days (Q1–3, 7–27 days). As shown in Figure 5, LOS showed a good linear relationship with median cost per patient ( $R^2=0.738$ ), and Spearman correlation coefficient revealed a strong and significant positive relationship ( $r=0.902$ ,  $p<0.001$ ).



**Figure 5** Plot graph illustrating the relationship between the length of stay and cost of treatment.

## Treatment Groups

When cultured, out of 227 patients (30.6%), there were no signs of growth for any organisms. In the case of 341 patients (46.0%), positive bacterial cultures were observed, while 156 patients (21.0%) exhibited fungal infections. A smaller portion, 10 patients (1.3%), showed positive cultures for viruses, and 7 patients (0.9%) had parasitic infections, all of which were caused by *Acanthamoeba* species. Table 5 compares clinical characteristics among patients with different culture results. For patients with negative and positive cultures, no statistically significant differences were observed in age at presentation, number of surgical treatments, LOS, and BCVA at presentation, with p-values of 0.086, 0.133, 0.955, and 0.698, respectively. Similarly, among patients with positive cultures, there were no statistically significant differences in these clinical characteristics, with p-values of 0.070, 0.630, 0.580, and 0.641, respectively. Table 6 presents a comparison of the direct MK treatment costs per patient in each cost category for inpatients, categorized by culture-proven causative organisms. There was no statistically significant difference (p-value 0.312) between the total direct treatment costs for patients with negative cultures (median US\$9998.88, Q1–Q3 US\$5580.95–21,660.23) and those with positive cultures (median US\$10,836.74, Q1–Q3 US\$5966.79–25,056.15). Regardless of whether the expenses were incurred as part of hospital services costs, medical professional services costs, investigation costs, operative treatment costs, or non-operative treatment costs (p-values 0.680, 0.984, 0.105, 0.604, and 0.263). Among culture-positive cases,

**Table 5** Comparison of Clinical Characteristics Among Patients with Different Culture Results

	Culture results						p-value <sup>a</sup>
	Negative	Positive					
		Bacterial	Fungal	Viral	Parasitic	p-value <sup>b</sup>	
N	227	341	156	10	7		
Male (N)	144	212	96	6	4	0.043*	0.648
Age at presentation (years; mean ± SD)	52.17 ±18.42	53.26 ±17.41	56.71+ 13.14	53.7± 22.16	52.63+ 17.65	0.070 <sup>d</sup>	0.086 <sup>c</sup>
Age group at presentation (N)						0.276	0.503
<30 years	26	33	15	2	0		
30–60 years	120	170	94	3	4		
>60 years	81	138	47	5	3		
Number of surgical treatments (N)						0.630	0.133
I TPK	44	69	33	1	1		
> I TPK	6	6	2	1	0		
Evisceration/ enucleation	40	43	21	0	1		
LOS (day; median, Q1–Q3)	12 (6–24)	12 (7–21)	12.5 (7–25)	10 (7–21)	7 (4–29)	0.580	0.955
BCVA at presentation (N)						0.641	0.698
≥ 20/60	11	12	4	0	0		
<20/60–20/200	18	31	14	2	0		
< 20/200–20/400	9	13	5	0	0		
<20/400	189	285	133	8	7		

**Notes:** <sup>a</sup>p-values were calculated using Mann–Whitney U-Test between culture-positive and culture-negative patients. <sup>b</sup>p-values were calculated using Kruskal Wallis test among culture-positive patients. <sup>c</sup>p-values were calculated using one-way ANOVA test between culture-positive and culture-negative patients. <sup>d</sup>p-values were calculated using Student's t-test among culture-positive patients. \*Significant p-value <0.05.

**Abbreviations:** N, number of patient(s); TPK, therapeutic keratoplasty; BCVA, best corrected visual acuity.

**Table 6** Comparison of Direct MK Treatment Costs for Inpatients Based on Culture-Proven Causative Organisms

	Culture Results						
	Negative N=227	Positive					p-value <sup>a</sup>
		Bacterial N=341	Viral N=10	Fungus N=156	Parasite N=7	p-value <sup>b</sup>	
Hospital services costs	137.20 (135.80–138.60)	137.20 (135.80–138.60)	137.90 (135.80–788.90)	137.20 (135.80–138.60)	138.60 (137.20–248.32)	0.310	0.680
Medical professional services costs	5487.86 (2649.50–9890.84)	5018.09 (2687.30–10,088.85)	6642.91 (752.43–3137.59)	5098.94 (2589.77–11,745.32)	5326.79 (495.49–1939.66)	0.918	0.984
Investigation Costs	1046.64 (718.04–1884.96)	1165.50 (741.65–2056.11)	1613.47 (752.43–3137.59)	1210.16 (826.01–2071.20)	731.11 (495.49–1939.66)	0.427	0.105
Operative treatment costs	1749.30 (908.60–3410.40)	1748.60 (980.00–3220.00)	2903.95 (990.76–4556.12)	1998.67 (1049.30–3849.30)	1505.00 (629.30–4865.00)	0.344	0.604
Non-operative treatment costs	2221.27 (852.05–5998.91)	2522.66 (981.18–6530.18)	2703.11 (820.95–6068.49)	2387.30 (955.94–7955.30)	2214.73 (323.92–7765.80)	0.981	0.263
Total direct costs	9998.88 (5580.95–21,660.23)	10,379.26 (5899.97–24,667.20)	13,221.54 (9525.82–24,206.07)	10,918.67 (6054.53–27,986.69)	20,117.29 (4268.88–25,102.11)	0.756	0.312

**Notes:** <sup>a</sup>p-values were calculated using Mann–Whitney *U*-Test between culture-positive and culture-negative patients. <sup>b</sup>p-values were calculated using Kruskal–Wallis test among culture-positive patients. N= number of patient(s). Values are presented in US\$ as median (Q1–Q3).

there was no statistically significant difference in direct healthcare costs in each category. However, it's worth noting that cases of parasite infections among culture-positive patients resulted in the highest expenditure for inpatient care, primarily in terms of medical professional services and non-operative care, with each of these being statistically non-significant at p-values 0.918 and 0.344, respectively.

## Discussion

This was a 7-year retrospective study investigating the economic burden of treating hospitalized MK and its associated factors. Over the past 7 years, Rajavithi Hospital spent approximately 14 million US\$ on treating 741 patients who initially presented with MK. The median cost per patient was US\$10,840.17 (US\$5866.56–24,172.28) which is higher than that of a previous study published in 2013 from Thailand (median cost per patient 20,699 THB = 673.55 USD, average exchange rate at the time of publication in 2013 of 30.731 THB/ 1 USD).<sup>14</sup> In the United States, MK costs the health care system an estimated 175 million dollars in direct health expenditure.<sup>5</sup> Compared with other countries, our median cost was higher than the average in Taiwan study in 2000–2013 (New Taiwan Dollar (NTD) 34,261.20 ± 40,906.62 (US\$ 1027 ± 1227.20), but lower than that found in a UK study in January to December 2013 (2855 British Pound (GBP) (US\$4465.22)).<sup>10,11</sup> Keay et al reported that the cost of treating contact lens -related MK was for severe cases with vision loss, 1596 AUD (US\$1085.28) for severe cases without vision loss, and 795 AUD (US\$540.60) for mild MK<sup>17</sup> (ANOVA,  $p = 0.001$ ). Another study in Belgium reported a mean total cost of 3093,19 EUR. US\$3835,56) for treating contact lens -related MK.<sup>18</sup> In reality, expenditure in different countries cannot be directly compared because of the varying costs of living, medication prices and guaranteed minimum incomes.

The highest cost incurred in treating one individual patient in our study was US\$156,048.35. This patient was initially admitted with MK at the eye department, but after 2 days, he developed hospital-acquired pneumonia and then sepsis. Due to his multiple underlying diseases, he was intubated and referred to an intensive care unit (ICU) where he received many systemic medications, blood transfusion and hemodialysis as required. Finally, he was safely discharged after spending 58 days in the hospital.

Hospitalization is one of the medical strategies that can help improve adherence to drug regimens. It is usually needed in difficult settings, such as with older age groups, with people who do not have access to means of transport, or individuals who lack adequate home healthcare. However, hospitalization may result in higher treatment cost, and it may also increase the risk of hospital-associated infection being transmitted to the patients, who could also face loss of income during their stay and possibly experience psychological problems. Many studies have revealed a reduction in the number of hospitalized COVID-19 cases due to lack of hospital beds, medical supplies and personnel.<sup>19,20</sup> Bhatt et al reported that the number of hospitalized cardiovascular patients markedly decreased during the COVID-19 situation, and patient LOS has also been shorter during this time.<sup>21</sup> However, ours is the first study to determine the reduction of hospitalized MK patients during the COVID-19 pandemic. Lowering LOS and accelerating patient discharge can yield multiple benefits in a variety of ways.<sup>22</sup>

As shown in Figure 3, total costs in 2020 displayed a significantly downward trend. The reason may be that, in Thailand as in other countries, we faced the pandemic crisis of COVID-19 throughout the entire year. The total cost burden declined as the number of patients markedly decreased; however, Figure 4 shows that the median cost per patient in 2020 rose above that of other years. This implies that, firstly, the hospitalized patients in 2020 were more severe cases and needed more treatment expense. Secondly, it reflects fact that the advent of the COVID-19 pandemic impeded the referral system by limiting our ability to transfer patients from peripheral to central areas, and some patients decided not to seek medical care in Bangkok hospitals due to the overcrowding resulting from the number of COVID-19 cases there. The implementation of self-treatment strategies or home health care could yield benefits, not only for patients but also for the hospitals.

In this retrospective study, the factors associated with higher costs included longer LOS, elderly, readmitted patients, DM, hypertension, and heart disease. LOS has been found in several studies to be the most significant factor affecting cost of medical care.<sup>10,14</sup> A study by Moussa et al concurred that longer LOS is significantly associated with higher cost deficit.<sup>10</sup> At Rajavithi Hospital, hospital and medical professional costs are charged at a fixed rate of 400 THB and 650 THB per day respectively. Therefore, the longer the patient stay, the higher the cost in both categories. Figure 5 also

explicitly shows a strong and significant linear correlation between LOS and medical cost per patient. The longest LOS was 86 days, and this was the case of a female who was hospitalized on 5 separate visits. She was treated with penetrating keratoplasty (PKP) at her first visit; unfortunately, the disease was not brought under control and became recurrent on the graft. Later, another PKP was performed, and the total cost of all treatment courses amounted to US \$109,087.03.

In our study, there was no statistically significant difference in the costs of treating males and females. Ballouz et al findings were in agreement with this, with gender not being associated with medical burden and treatment length.<sup>23</sup> Another study from Taiwan, in contrast, reported that male gender predominated in an IPD group.<sup>11</sup> The mean age of patients in this research was 52.4 years, but people of all ages have been shown to be affected by MK, and in our study, the age at the presentation ranged from 7 to 95 years old. The age group causing highest treatment expense was patients aged more than 60 years, and this is similar to the results of a previous study from Koh et al, who found that highest health care expenditure was incurred in treating those older than 65 years. They also reported that patients older than 40 years of age accounted for approximately 80% of the cost of treating MK.<sup>11</sup> However, Boonpasart et al, who conducted a study in King Chulalongkorn Memorial Hospital, Thailand, found that the majority of patients were in the age groups 21–30 and 51–60 years of age.<sup>24</sup>

Regarding VA at initial presentation, we firstly hypothesized that worse VA would result in higher median costs per patient; however, statistical differences were identified only between moderated visual impairment VS severe visual impairment group and moderate visual impairment VS blindness group. This could be because the number of patients in the group with blindness was markedly larger than those of other groups.

The culture positivity rate in the literature varies, ranging between 24% and 77%.<sup>2,5,6,25–27</sup> Despite our clinic's status as a tertiary referral center and the fact that the majority of our patients were referred after receiving broad-spectrum antimicrobial therapy prior to presentation, we observed a positive culture rate of 69.4%. This rate aligns with the existing literature and represents a relatively high percentage. Our study revealed that among culture-positive patients, bacteria were the most common causative agents, accounting for 66.3% of cases, followed by fungal infections at 30.4%. This finding is consistent with previous research findings in Thailand.<sup>7,28</sup> The predominant age group in both culture-positive and culture-negative patients was 30–60 years old. This observation aligns with the higher prevalence of MK within this age range, likely due to increased exposure to relevant risk factors. This finding is consistent with a comprehensive review of 14 epidemiologic studies conducted across diverse regions, including Asia, the United Kingdom, Europe, North America, South America, Africa, the Middle East, and Australia. The review highlighted a consistent trend, with the majority of MK cases occurring in individuals aged 30 to 55 years.<sup>2</sup>

Regarding treatment modalities, 63.8% of patients in our study received medical therapy alone, while 36.2% required surgical interventions such as therapeutic keratoplasty or evisceration/enucleation. Interestingly, no significant difference was found in the frequency of surgical interventions between the culture-positive group (34.6% of 514 patients) and the culture-negative group (39.6% of 227 patients). These results are in line with some previous studies that also compared culture results.<sup>29,30</sup> However, it's worth noting that certain other studies have reported a higher need for surgical intervention in the culture-positive group compared to the culture-negative group.<sup>31–33</sup> These discrepancies may be attributed to variations in demographic data and risk factors among the study populations.<sup>29,31</sup>

In our study, we found that the median direct cost for treating a single episode of severe keratitis was US\$10,840.17, with an interquartile range spanning from US\$5866.56 to US\$24,172.28. Notably, there was no significant difference in direct costs observed between cases with negative cultures and those with positive cultures. Among the latter group, individuals with parasitic infections incurred the highest direct costs, primarily due to expenses related to medical professional services. However, our statistical analysis did not reveal a significant difference in costs among the culture-positive cases. All the parasite cultures in our study were determined to be *Acanthamoeba* species. The treatment for *Acanthamoeba* keratitis typically involves the administration of multiple medications. These medications encompass a range of antimicrobial drugs such as chlorhexidine, propamidine, as well as other therapeutic agents including analgesics, cycloplegics, and sometimes antifungal agents.<sup>34,35</sup> Importantly, the cost of these medications can accumulate significantly, especially if they must be used over an extended period.

Radhakrishnan et al reported that fungal keratitis carries the highest treatment costs compared to other types of infections, primarily due to its prolonged treatment duration and the elevated expenses associated with antifungal medications.<sup>36</sup> We did not identify any statistically significant differences in the total cost of treating MK between patients with positive cultures and those with negative cultures. Additionally, among the subset of patients with positive cultures, we found no statistically significant distinctions in terms of medical professional costs, which constitute the primary expense in the treatment of MK. This observation may help explain the similar LOS between culture-negative and culture-positive patients in our study. The median LOS was 12 days for culture-negative patients, 12 days for bacterial infections, 12.5 days for fungal infections, 10 days for viral infections, and 7 days for parasitic infections. These comparable LOS figures suggest that the duration of hospitalization, a significant contributor to medical professional costs, was similar for both culture-positive and culture-negative patient groups in our research. Koh YY found that DM was associated with severity of condition requiring hospitalization or surgical interventions.<sup>11</sup> Our study showed that higher costs were incurred not only in treatment of DM, but also of hypertension and heart disease.

Our goal in treating MK is to control infection and to limit visual impairment. Nevertheless, the economic burden both direct (ie diagnostic disorder, vision aids or devices, undiagnosed vision loss, educational, assistance programs) and indirect (ie productivity loss, informal care, nursing home, entitlement programs, tax deductions, transfer deadweight loss, and the constraints of salary during hospitalization) should also be considered.<sup>37</sup> The health care coverage system was derived mainly from the government's policy statement on expenditure, and as the government is responsible for paying for all standard health expenses of the Thai population, the ability to achieve a balance between costs and treatment outcomes is a primary concern affecting patients, physicians, and policymakers alike.

## Strength and Limitations

This study provides the up-to-date treatment cost of MK for the past 7 years, including the COVID-19 situation. In considering 741 patients, this is one of the largest studies performed to evaluate the cost of MK treatment. We also indicate the primary sources of cost by classifying the subgroups of cost. With regard to limitations, firstly, this study may have underestimated the true cost of treating MK by omitting the non-hospitalized patients who were treated as OPD cases. COVID-19 markedly reduced the number of hospitalized patients, so this study's findings may not truly reflect the real-world situation of MK, but it does raise some question regarding the current treatment strategy. Secondly, we included both MK-related and non-MK-related treatment cost; for example, the costs of treating unfavorable complications were also included for all patients which, overall, may have been an overestimation. Thirdly, since all cases in the study were categorized as severe MK, necessitating hospitalization. We did not endeavor to calculate the treatment costs across varying severity levels. It's evident that managing mild and moderate MK cases would incur lower expenses due to the absence of hospitalization, potentially resulting in reduced treatment costs for MK at different severity levels. Fourthly, we gathered data on all eligible patients from their admission to the hospital until their discharge. The study did not encompass the direct cost of ongoing treatment in the outpatient department until their microbial keratitis was fully healed or until evisceration/enucleation took place. It's evident that the total direct treatment cost until complete healing of their MK might surpass what has been reported in this study. Lastly, the study's retrospective nature was another limiting feature.

## Conclusion

Our findings highlight several key factors impacting the direct healthcare costs of severe microbial keratitis treatment. Notably, medical professional services emerged as the most substantial cost category, while longer hospital stays, older age groups, readmission cases, and comorbidities such as diabetes mellitus, hypertension, and heart disease were all linked to elevated treatment expenses. Remarkably, there were no statistically significant differences in the direct medical expenses associated with treating severe MK, whether the culture results were positive or negative, or regardless of the type of cultured organism utilized.



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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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