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Cost-effectiveness of an adherence-enhancing intervention for gout based on real-world data

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Abstract

Aim: Medication non-adherence influences outcomes of therapies for chronic diseases. Allopurinol is a cornerstone therapy for patients with gout; however, non-adherence to allopurinol is prevalent in Singapore and limits its effectiveness. Between 2008-2010, an adherence-enhancing program was implemented at the rheumatology division of a public tertiary hospital. The cost-effectiveness of this program has not been fully evaluated. With healthcare resources being finite, the value of investing in adherence-enhancing interventions should be ascertained. This study aims to evaluate the cost-effectiveness of this adherence-enhancing program to inform optimal resource allocation toward better gout management.

Method: Adopting a real-world data approach, we utilized patient clinical and financial records generated in their course of routine care. Intervention and control groups were identified in a standing database and matched on nine risk factors through propensity score matching. Cost and effect data were followed through 1-2 years. A decision tree was developed in TreeAge using a societal perspective. Deterministic and probabilistic sensitivity analyses were performed to assess parameter uncertainty.

Results: At an assumed willingness-to-pay threshold of $50 000 USD ($70 000 SGD) per quality-adjusted life year (QALY), the intervention had an 85% probability of being cost-effective compared to routine care. The incremental cost-effectiveness ratio was $12 866 USD per QALY for the base case and ranged from $4 139 to $21 593 USD per QALY in sensitivity analyses.

Conclusion: The intervention is cost-effective in the short-term, although its long-term cost-effectiveness remains to be evaluated.

KEYWORDS

allopurinol, cost-effectiveness analysis, electronic medical records, gout, medication adherence, quality-adjusted life year

1 | INTRODUCTION

1.1 | Gout overview and treatment

Gout is the most prevalent form of inflammatory arthritis among adults, with long-term impact on patients' health, quality of life, and health services utilization.[1-3] It arises from persistently high serum urate (SU) levels leading to crystallization around joint structures. Deposition of monosodium urate crystals not only causes acute episodic gouty arthritis

(also called attacks or flares) but results in progressive joint damage.[4,5] Left untreated, patients experience increasing frequency and longer duration of recurrent flares, impairment to kidney function, and deposition of urate crystals in the form of tophi within joints, tendons and under the skin.[6] Some patients are unable to perform daily tasks or remain gainfully employed, thus affecting economic productivity.[5]

Singapore is a city-state in Southeast Asia, home to a population of 5.5 million.[7] The prevalence of gout in Singapore is 4.1%, higher than estimates in North America and Europe of between 1%-4%.[8,9] Allopurinol, a highly effective xanthine-oxidase inhibitor is the first-line long-term urate-lowering therapy (ULT) for gout when attacks become recurrent or in the presence of tophi, arthritis, renal impairment or urolithiasis.[10] Reduction and maintenance of SU below 360 μmol/L prevent further gout attacks and promote tophi shrinkage.[6,11,12] Today, allopurinol remains the primary and most commonly prescribed option in Singapore (95%) for chronic management of gout due to lack of alternatives until the recent introduction of febuxostat.[13,14] Uricosuric agents such as probenecid and benzbromarone are locally rarely used. Long-term adherence to ULT limits the damaging impact of gout on daily living activities.[2,3,15]

1.2 | Medication adherence: "Drugs don't work in patients who don't take them"

Poor or non-adherence counteracts the effectiveness of allopurinol and poses a major barrier to gout management.[6,11,16] A World Health Organization report on adherence concluded that patients with chronic diseases are only on average 50% adherent in real-world settings.[17] More recently, medication adherence was compared across seven common chronic conditions including hypertension (72%), hypothyroidism (68%) and diabetes mellitus (65%), and reported that adherence levels were lowest in gout (37%).[18] The urgency to address this is compounded by a rapidly growing burden of disease, observed in Singapore and worldwide.[4]

Only 24% of Singaporean patients on gout medication are highly adherent based on their Morisky Medication Adherence Scale-8 (MMAS-8) score, a validated patient self-report scale that has been found to reliably assess and predict patient medication-taking behavior.[19] Another local study based on clinical outcome measures (whether patients achieve target SU levels) found that only 25% of patients had controlled SU levels during 1 year of regular care. The authors cited poor patient adherence to allopurinol as a significant problem.[14]

1.3 | Determinants of medication non-adherence

Reasons for patients to forego medications as prescribed are complex, as non-adherence may be intentional or unintentional.[20-22] In Bae et al's framework (Figure 1), patient beliefs about medicines and self-efficacy are proximal pathways to non-adherence, while sociodemographics, illness-related status, and polypharmacy are distal drivers.[20,23] Distal factors are contextual characteristics of the patients that influence their cognition and beliefs, which in turn impact non-adherent behavior.

In Singapore's context, patient knowledge, beliefs, and attitudes toward ULT often predict non-adherence.[24] Traditionally, gout has been trivialized as a disease that does not impact mortality and morbidity.[13,14,24] Many view gout as episodic and mistakenly discontinue ULT after symptomatic treatment.[14] Perceived or experienced adverse effects also deter patients and prescribers, especially as ULT can trigger acute flares when first initiated.[11,13,19,24,25] Additionally, poor self-conviction in being able to successfully execute adherent behavior (ie low self-efficacy) has been linked to non-adherence.[11,26]

Other significant predictors of non-adherence among Singaporeans with gout include presence of comorbidities, patient marital status, and education level.[19,24] Consistent with the published literature on gout, local patients with comorbidities tend to be more adherent.[6,18] It has been suggested that patients who are more proficient in managing chronic conditions become better adherers.[6] Comorbidities also signal more life-threatening conditions that realign patient attitudes toward adherence.[19] Married individuals are also more likely adherent because of practical support from spouses in taking medication.[24,27] Notably, gout patients with formal education in Singapore are found to be less adherent and possibly more critical of advice from their doctors.[19]

1.4 | Cost-effectiveness studies of adherence-enhancing interventions in gout

Only a handful of studies have evaluated the cost-effectiveness of investing in interventions that address non-adherence. Not surprisingly, none of them are in gout.[28-31] In one systematic review, cost-effectiveness analyses (CEA) for 12 counselling adherence-enhancing interventions were inconclusive. Although 10/12 counselling interventions were highly cost-effective or cost-saving, there

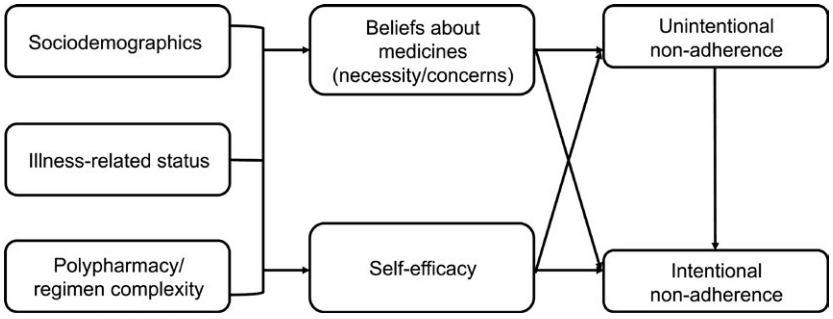

FIGURE 1 Non-adherence framework adapted from Bae et al[20]

were two interventions that were less effective and more costly than standard care ("dominated").[28]

Between 2008-2010, an adherence-enhancing program for patients with gout was implemented in the rheumatology division of a tertiary hospital in Singapore (the National University Hospital; NUH).[14] The clinical practice improvement program (CPIP) aimed to improve gout management and address issues that promoted allopurinol non-adherence. A counselling component focused on health education, patient empowerment, and self-management training during acute attacks. Patient education targeted misguided beliefs regarding ULT and aimed to improve self-efficacy. Patients were referred to dietitians and had telephone access to rheumatology nurses. Counselling was supplemented by titration of allopurinol according to SU laboratory test results, and by increasing the frequency of patient follow-ups until the target SU of 360 μmol/L was achieved. Patients who failed to attend their clinic appointment were called by nurses to improve follow up or perform lab tests and refill prescriptions.

The feasibility and effectiveness of the 1 year program in 126 patients was demonstrated by the percentage of patients who were treated-to-target increasing from 25% to 56%. However, the intervention's value for money has not been evaluated.[14] Lim et al's study estimated, with a basic cost analysis, that the cost of the intervention program ($500 Singapore dollars/y; SGD) was less than the cost of avoided hospitalizations (anecdotally $4200-4500 SGD/y).[14] Building on their work, additional rigor in evaluating the program's outcomes with CEA enables us to assess whether the CPIP is cost-effective.

Key components of the NUH gout clinical improvement program have become standard practice in the division today. Current program funding would be justified if it is found that the intervention is cost-effective, and would encourage further investment to improve its design or broaden its outreach. This study's aim is to assess the cost-effectiveness of the CPIP intervention in 2008-2010, in order to provide an additional and important dimension of consideration when evaluating its success in improving allopurinol adherence among Singaporean patients with gout.

2 | METHODS

2.1 | Propensity score matching

Lim et al's study enrolled 126 adult gout patients presenting at the NUH rheumatology clinic.[14] Patients were eligible if they had fulfilled indications for ULT with allopurinol, that is: frequent gout attacks; presence of tophi, radiographic erosions or nephrolithiasis; and hyperuricemia with SU levels >360 μmol/L.[14] As their study was unable to perform randomization and collect control group data due to ethical and resource considerations, we aimed to reanalyze the effectiveness of the program using the hospital's Patient Affordability Simulation System (PASS) database. PASS is a 10-year standing database for historical patient electronic medical records (EMR), pharmacy data on prescription orders and fulfillment, and financial transactions. PASS records have been routinely collected as part of hospital administration and clinically indicated procedures. With this methodology, the adherence intervention can be evaluated not only for patients enrolled by researchers in the study, but all patients during this period who have undergone the intervention. As such, the real-world evidence (RWE) in PASS provides insight into disease and treatment patterns in real-world practice settings.[32]

Intervention cases were selected based on criteria which closely mirrored the original study (N = 111). These were: (a) patient in attendance at the outpatient rheumatology clinic within the CPIP enrollment period of December 2008 to December 2009; (b) having a first allopurinol prescription on that visit, thereby known as their study entry and index date; (c) an uncontrolled SU test value >360 μmol/L on the index date; and (d) having at least one SU test within their follow-up duration to qualify for inclusion. Control group patients were selected from gout patients treated in subspecialties at NUH other than rheumatology within the same time frame, where the condition is treated alongside comorbidities in nephrology, cardiology, and general medicine (N = 198). To generate comparable intervention and control groups from PASS, propensity score matching (PSM) was used to match a case with a closest-related control based on propensity scores that account for measured confounders.[33] These include matching on underlying patient characteristics and risk factors in Bae et al's framework (Figure 1) known to influence non-adherence.[20] More concretely, the matching variables we chose for PSM included demographics (age, sex, ethnicity), comorbidities (Charlson comorbidity index), SU at baseline, gout hospitalization history at baseline, and gout medication use (non-steroidal anti-inflammatory drugs [NSAID], colchicine, glucocorticoids).[14,34]

Data for matching variables were extracted from the PASS database for 111 intervention and 198 control patients. Demographics and SU were assessed on the index date: gout medications from 6 months prior, and comorbidities and hospitalization from 1 year prior to the index date. PSM was conducted using the MatchIt package in R (The R Foundation for Statistical Computing, http://www.r-project.org/).[35] We adopted a nearest-neighbor, 1-to-1 method of matching.[36] A "caliper" of 0.25 standard deviations, otherwise known as the maximum permitted distance between matched subjects, is commonly used and was thus chosen for the PSM.[37] Detailed methodology and assumptions used for patient selection and the PSM variables can be found in Appendix S1.

2.2 | Economic evaluation and decision tree analysis

2.2.1 | Design, perspective, and time horizon

A decision tree analysis was developed using TreeAge (TreeAge Software, Inc Williamstown, MA) to evaluate the incremental cost-effectiveness of the intervention for gout patients attending NUH rheumatology compared to the other clinics.[14] Decision tree analysis was chosen over Markov modeling methods as the time horizon of the analysis was short and in the absence of repeated actions or with time-dependent events.[38] Cost analyses were evaluated in SGD

then presented in USD, and effectiveness in quality-adjusted life years (QALYs). One SGD = 0.71 USD with the currency exchange rates on 10 April 2017.[39] In the base case, the societal perspective was used such that indirect costs significant in chronic diseases were included. The time horizon was 1 year, defined from the index date of the patient's first prescribed allopurinol. Sensitivity analysis was conducted for the hospital perspective and with an extended follow-up of 2 years.

2.2.2 | Intervention effect

The clinical database linked to the electronic medical records was reviewed for SU outcomes, defined as the last SU test value within the patient's follow-up period. Patients were stratified according to the degree to which they were treated-to-target. The intervention effect of the CPIP was measured by the percentage of patients at target (≤360 μmol/L) upon the end of follow-up in both groups.[14]

2.2.3 | Costs

Direct medical costs for matched patients were extracted from the finance data in the PASS database for their gout-related inpatient and outpatient services. Hospitalization for acute gout flare episodes were identified with the International Classification of Diseases 9-CM code 274 for primary diagnoses. Consumed hospital services for each inpatient admission was reviewed by a pharmacist blinded to the treatment group for further confirmation of gout relevance. Outpatient costs included gout-specific cost items in the database for six categories (full list in Appendix S2). Medical costs for comorbidities were not included as comorbid conditions were not different between groups after PSM matching. Direct non-medical costs, for example transport, were excluded as earlier data from local rheumatoid arthritis patients showed that its contribution to societal cost was less than 2%.[40]

Costs evaluated from the hospital's perspective were taken to be the sum of inpatient and outpatient direct costs. Indirect costs based on a human capital approach were included for societal perspective analyses, costing for lost income and the monetary value of employer-paid benefits lost during sick leave.[38] Details for costing of productivity losses and its assumptions can be found in Appendix S2. Inflation using Singapore's Consumer Price Index was applied to adjust costs to their 2016 values.[41] Discounting for costs and effects was not performed due to the short follow-up of 1 or 2 years.[38] Internal verification of costs was ensured by double programming for estimation of inpatient costs, with two programmers independently using R 3.2.5 and Stata 14.0 (StataCorp LLC, College Station, TX, USA).

2.2.4 | Effects: Utilities and quality of life

Utility estimates of different health outcomes were applied based on patient SU levels at baseline and end of follow -up. Final SU test values were grouped into four bands: ≤360 μmol/L, >360 and ≤480 μmol/L, >480 and ≤600 μmol/L, and >600 μmol/L. SU at target (ie ≤360 μmol/L) was assigned the utility of 0.746, which decreases by 0.034 with every increment of 120 μmol/L.[2,3] The utility of a death event was assumed to be 0.[2] These weights, provided by a multi-country study by the Institute of Medical Science using the EuroQoL 5 Dimensions (EQ-5D), have been used by other Singaporean publications in the absence of locally established utility values for patients with gout.[3,42]

2.2.5 | Model structure and CEA

The sum of the costs and QALYs per patient associated with each clinical outcome (SU bands, and all-cause mortality) was computed at the end of the follow-up duration (Figure 2). Transition probabilities were estimated by the proportion of patients in each group by the end of the study. To determine the cost-effectiveness of the intervention, an incremental cost-effectiveness ratio (ICER) summarized the CEA result by dividing the incremental cost (ΔC) by the incremental QALYs (ΔE). There is no official threshold in Singapore for reimbursement decisions, but the intervention was taken to be cost-effective if the ICER was below $50 000 USD, a commonly used willingness-to-pay (WTP) threshold for health economics research in Singapore and worldwide.[42,43] This is approximately $70 000 SGD/QALY based on the $1 USD = $1.41 SGD currency exchange rate on 10 April 2017, provided by the Monetary Authority of Singapore.[39]

Uncertainty of model parameters was assessed with sensitivity analyses (SA). In deterministic SA, ±95% confidence intervals of cost and effect drivers were used as the lower and upper bounds for the SA. The order of impact of the variables on the ICERs was evaluated with a Tornado diagram. Scenario analyses for selected base case assumptions were also tested for their impact on the results. These were: (a) societal versus hospital perspective; (b) 1 vs 2 years of follow-up; and (c) 0.5 vs 1 day sick leave assumed per unique outpatient visit for estimating productivity losses arising from gout.

A Monte Carlo simulation of 10 000 iterations was used in a probabilistic sensitivity analysis (PSA). PSA was performed to check the simultaneous effect of uncertainty in the model. Using means and standard deviations taken for each of our clinical outcomes, we applied gamma distributions for cost variables and beta distributions for effects. A summary of parameter uncertainty was presented in a cost-effectiveness acceptability curve (CEAC). Given the cutoff WTP, the CEAC returns the probability of iterations wherein the results were cost-effective.

3 | RESULTS

3.1 | Propensity score matching

Propensity score matching (PSM) on nine variables resulted in 106 patients, with a sample of 53 in each group. Table 1 summarizes univariate tests of independence on baseline characteristics before and after PSM. Before matching, the intervention sample was significantly younger ($P < 0.05$), had more males ($P < 0.01$), higher use of NSAIDs, colchicine, glucocorticoids ($P < 0.001$), and more frequent gout admission history ($P < 0.01$). Controls were more often with

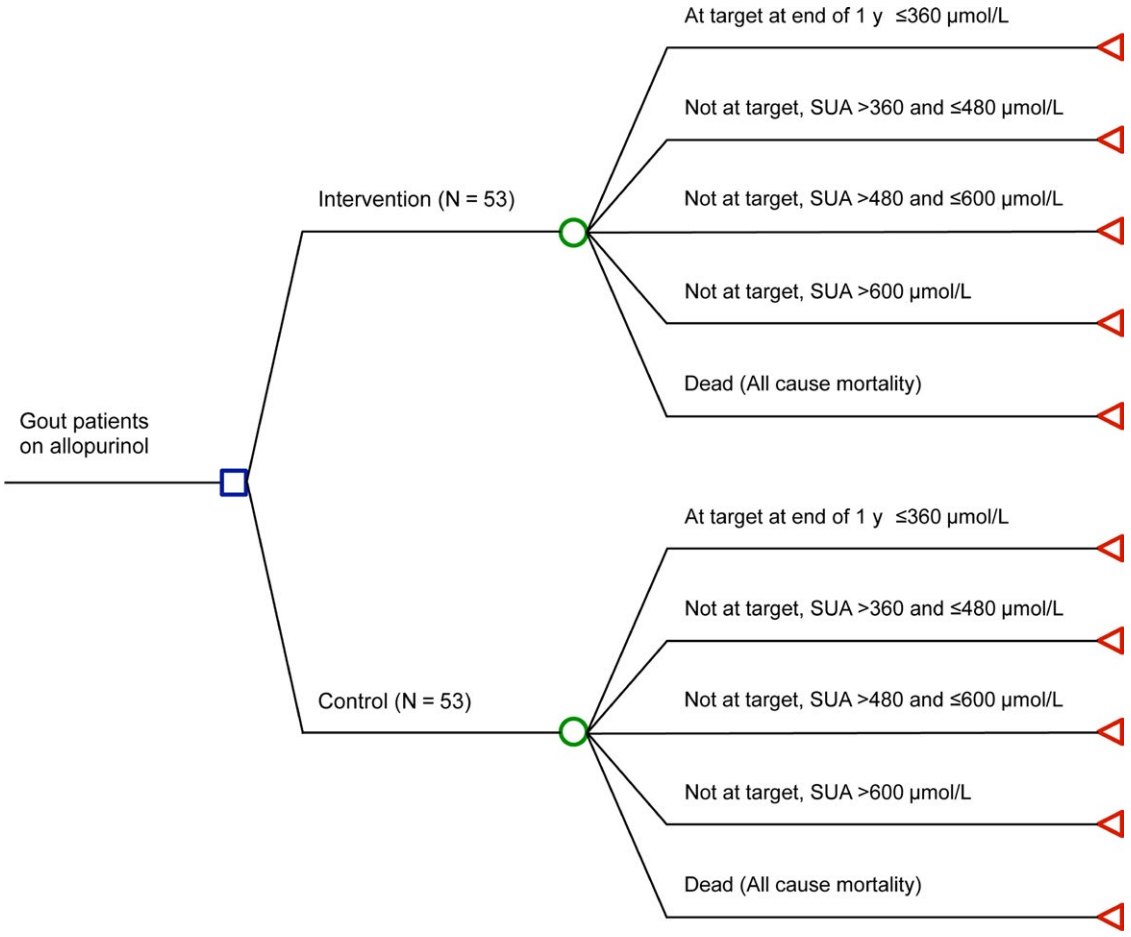

FIGURE 2 Decision tree model structure

comorbid conditions such as diabetes ($P < 0.01$) and chronic kidney disease ($P < 0.05$). The results of the PSM showed that differences in glucocorticoid use between groups remained marginally significant post-matching ($P = 0.0448$). No other variables at baseline were found to be statistically different between intervention and controls after matching.

3.2 | Economic evaluation and decision tree analysis

The decision tree was populated with costs, effects, and transition probabilities from PASS. The complete dataset for the model input can be found in Appendix S3. There were no missing values. For the intervention effect, 32% of rheumatology patients were treated-to-target by the end of 1 year, compared to 17% of controls from the other clinics.

3.2.1 | Base case analysis

The CPIP intervention was cost-effective with an ICER of $12 866 USD/QALY in the base case using the 1 year follow-up period and the societal perspective for analysis (Table 2). Patients in the intervention group incurred higher cost in all three cost components (inpatient, outpatient, and productivity losses).

3.2.2 | Sensitivity analyses

All SA on model parameters produced ICERs below the chosen threshold value for cost-effectiveness. The key driver for cost-effectiveness based on Tornado analysis, that is the input parameter that leads to the most uncertainty in the ICER when varied, was inpatient cost ($4139–$21 593 USD/QALY). The least sensitive variable was outpatient cost ($12 798–$12 932 USD/QALY). Table 3 summarizes results from scenario analyses of various deviations in assumptions from the base case. When the perspective was changed from societal to hospital, the ICER decreased 28% from $12 866 to $9296 USD/QALY. Two-year follow up also decreased the ICER by 37% to $8151 USD/QALY, suggesting maintenance of the intervention effect and cost-effectiveness over time. Applying 1 day of sick leave per unique outpatient visit vs 0.5 days (base case) increased the ICER by 23% to $15 873 USD/QALY. All results from the scenario analyses were below WTP threshold.

3.2.3 | Probabilistic sensitivity analysis

Mean incremental cost for 10 000 iterations of the ICER increased by $8 USD from the result in the base case analysis, but mean incremental effect remained unchanged (Table 4). The majority of the simulations showed positive incremental effectiveness, hence the

TABLE 1 Baseline characteristics of intervention and control groups (A) before (top) and (B) after propensity score matching (bottom)

	Intervention (N = 111)	Control (N = 198)	*P* value[a]
A. Groups before propensity score matching			
Age, mean (SD)	57.44 (16.31)	62.80 (13.90)	<0.05*
Ethnicity, n (%)			
Chinese	69 (62.2%)	143 (72.2%)	
Malay	27 (24.3%)	33 (16.7%)	
Indian	3 (2.7%)	6 (3.0%)	
Others	12 (10.8%)	16 (8.1%)	
Sex, n (%)			
Male	91 (82.0%)	135 (68.2%)	<0.01**
Comorbidities, n (%)			
Charlson comorbidity index, mean (SD)	0.56 (1.51)	1.23 (4.21)	
Diabetes	1 (0.9%)	18 (9.1%)	<0.01**
Hypertension	2 (1.8%)	13 (6.6%)	
Chronic kidney disease	3 (2.7%)	18 (9.1%)	<0.05*
Ischemic heart disease	9 (8.1%)	8 (4.0%)	
Hyperlipidemia	0 (0%)	2 (1.0%)	
Cerebrovascular disease	2 (1.8%)	4 (2.0%)	
Medications, n (%)			
NSAIDs	35 (31.5%)	8 (4.0%)	<0.001***
Colchicine	101 (91.0%)	49 (24.8%)	<0.001***
Glucocorticoids	46 (41.4%)	31 (15.7%)	<0.001***
Gout admissions history, mean (SD)			
No. of hospitalizations at baseline	0.26 (0.55)	0.02 (0.14)	<0.01**
Laboratory measures, mean (SD)			
Serum urate	493.58 (96.77)	500.45 (119.25)	
	Intervention (N = 53)	**Control (N = 53)**	***P* value[a]**
B. Groups after propensity score matching			
Age, mean (SD)	59.25 (17.65)	61.3 (15.12)	
Ethnicity, n (%)			
Chinese	39 (73.6%)	40 (75.5%)	
Malay	8 (15.1%)	9 (17.0%)	
Indian	1 (1.9%)	1 (1.9%)	
Others	5 (9.4%)	3 (5.7%)	
Sex, n (%)			
Male	39 (73.6%)	39 (73.6%)	
Comorbidities, n (%)			
Charlson comorbidity index, mean (SD)	0.60 (1.81)	0.66 (1.62)	
Diabetes	1 (1.9%)	2 (3.8%)	
Hypertension	1 (1.9%)	3 (5.7%)	
Chronic kidney disease	1 (1.9%)	2 (3.8%)	
Ischemic heart disease	3 (5.7%)	1 (1.9%)	
Hyperlipidemia	0 (0%)	2 (3.8%)	
Cerebrovascular disease	1 (1.9%)	2 (3.8%)	

(Continues)

TABLE 1 (Continued)

	Intervention (N = 53)	Control (N = 53)	*P* value[a]
Medications, n (%)			
NSAIDs	6 (11.3%)	6 (11.3%)	<0.05*
Colchicine	45 (84.9%)	46 (86.8%)	
Glucocorticoids	18 (34.0%)	9 (17.0%)	
Gout admissions history, mean (SD)			
No. of hospitalizations at baseline	0.23 (0.61)	0.06 (0.23)	
Laboratory measures, mean (SD)			
Serum urate	481.91 (106.16)	491.62 (123.99)	

NSAIDs, non-steroidal anti-inflammatory drugs

[a]For continuous variables, 2-sample *t* tests were used if the variables fulfilled assumptions of normality and equal variances. Wilcoxon rank sum tests were applied if variables failed normality assumptions, and the Kolgomorov-Smirnov test if variables had failed both assumptions. Pearson's Chi-squared test was used for categorical variables as well as the Fisher's exact test for variables with expected cell counts of <5. Note: *p<.05, **p<.01, ***p<.001.

TABLE 2 Base case results. Costs are in USD at 2016 prices. $1 USD = $1.41 SGD[39]

	Intervention (N = 53)	Control (N = 53)	Increase difference
Costs USD per patient	738	487	251
Inpatient cost	140	35	105
Consultations, ward facilities	100	22	78
Diagnostic imaging	6	1	5
Lab investigation	8	1	7
Prescribed medications	13	6	8
Procedures, special investigations	5	4	2
Therapy	7	1	7
Outpatient cost	354	277	76
Consultations and facilities	240	207	33
Diagnostic imaging	12	6	6
Intervention	14	0	14
Lab investigation	6	2	5
Prescribed medications	80	52	28
Therapy	1	10	-9
Productivity cost	244	174	70
Effectiveness QALYs per patient	0.703	0.683	0.020
ICER (Increase USD/increase QALY)	$12 866 USD/QALY		

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

uncertainty relates largely to incremental cost. For greater precision, the proportion of iterations that were found to be cost-effective was determined over a range of WTP cutoffs and were presented using CEAC. The intervention had an 85% probability of being cost-effective at the threshold used in our analysis.

4 | DISCUSSION

This study set out to retrospectively evaluate the cost-effectiveness of an adherence-enhancing intervention for Singaporean patients with gout, using real-world data. We replicated Lim et al's results for the intervention's clinical effectiveness. In addition, findings from the present study showed a robust CEA result below the $50 000 USD/QALY WTP threshold, with high (85%) probability of being cost-effective when model parameters were varied. The intervention was cost-effective in the base case ($12 866 USD/QALY), and the ICER ranged from $4139 to $21 593 USD/QALY in sensitivity analyses. Despite cost of productivity losses being the second-most sensitive parameter of the CEA model, changing our fundamental assumptions about productivity in the scenario analyses did not alter the result beyond the WTP

TABLE 3 Scenario analyses. $1 USD = $1.41 SGD[39]

Condition	Cost (USD)	ΔCost	Effect (QALYs)	ΔEffect	ICER (ΔCost/ΔEffect)
Base case 1-y follow up, societal					
Intervention	738	251	0.703	0.020	$12 866 USD/QALY
Control	487		0.683		
SA hospital perspective					
Intervention	494	182	0.703	0.020	$9296 USD/QALY
Control	312		0.683		
SA 2-y follow up, societal					
Intervention	1124	373	1.390	0.046	$8151 USD/QALY
Control	750		1.344		
SA productivity loss is not 0.5, but 1 d per outpatient utilization					
Intervention	965	310	0.703	0.020	$15 873 USD/QALY
Control	655		0.683		

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; SA, sensitivity analysis.

TABLE 4 Probabilistic sensitivity analysis summary. Costs and thresholds are in USD

Condition	Cost (USD)	ΔCost	Effect (QALYs)	ΔEffect	ICER (ΔCost/ΔEffect)
Base case 1-y follow-up, societal					
Intervention	738	251	0.703	0.020	$12 866 USD/QALY
Control	487		0.683		
PSA 1-y follow up, societal, mean of 10 000 iterations					
Intervention	747	259	0.703	0.020	$13 278 USD/QALY
Control	487		0.683		

QALY, quality-adjusted life years; PSA, probabilistic sensitivity analysis

threshold. The overall percentage changes of 23%-28% in the ICER suggest that the model remains robust to alternative productivity assumptions, strengthening the cost-effectiveness result. Our ICER is consistent with two counselling interventions in the USA with incremental cost-effectiveness ratios of $16 117 and $18 133 USD/QALY in 2016 dollars.[44,45] The first had targeted adherence in geriatric conditions and the other in human immunodeficiency virus. Nevertheless, those models bear similarities to the present study as they adopted societal perspectives and used routine care as the choice of comparator. These findings add to the body of evidence that support the cost-effectiveness of counselling in adherence-enhancing interventions, particularly in the context of chronic disease management.

Incremental cost-effectiveness in the base case was not a novelty effect, where behavioral changes result from interest in a novel treatment. Cost-effectiveness could be maintained over an extended follow-up period of 2 years. Several factors may account for this trend. Innovation is disruptive to routine and shorter time horizons tend to ignore a learning curve effect.[46] Health professionals learn to be more efficient over time, thus costs in the early stages of intervention may not be good predictors of costs in the long run.[38] At the same time, allopurinol's therapeutic effect is not immediate. Patients take a few months to feel its full benefits and may experience increased frequency of gout attacks when the drug is 1st initiated, delaying evidence of its effectiveness.[24,25]

The model was most sensitive to varying the inpatient cost parameter. The ICER was impacted the most if inpatient costs were further increased or decreased. One reason may be the wide confidence interval in the data from a small 6% of patients requiring gout-related hospitalizations, which contributed 15% to total societal cost. We observed that inpatient costs remained higher among intervention patients than for controls for the two follow-up durations. Despite matching for other illness-related determinants like SU and inpatient events at baseline, intervention patients may remain at a higher risk than controls to develop acute gout flares, given that rheumatology patients post-matching had significantly higher usage of glucocorticoids (Table 1). Nevertheless, these observations are based on a very small number of inpatient events.

Additionally, there was concern that using PSM to create balanced comparison groups selected for patients of overall lower gout severity and fewer comorbid conditions. The original treatment group had a higher mean gout hospitalization history and acute gout prescriptions, and controls had more comorbidities (Table 1). After matching, the proportion of intervention patients taking NSAIDs at baseline was reduced from 32% to 11%. The control group's mean

Charlson comorbidity index decreased from 1.23 to 0.66 to match fewer comorbidities seen in the intervention group. While this limits the CEA findings to a specific subgroup with gout, our findings remain relevant. Studies suggest that healthier patients adhere poorly due to relative inexperience in chronic disease management.[6,47] A cost-effectiveness finding despite a low severity, low comorbidity, and possibly a less adherent patient population would strengthen the conclusion that the intervention has value for patients as well as the hospital.[24]

Comparison of outcomes from this study and Lim et al's support that healthier patients of lower disease severity are poorer adherers. The baseline proportion of intervention patients using NSAIDs was lower in our study which used PASS (11%), compared to Lim et al's recruited patients (44%).[14] Our patients were healthier, but Lim et al found a larger 31% increase (56% minus 25%) in the proportion of individuals achieving target SU due to CPIP, compared to our 15% (32% minus 17%).[14] Differences in disease severity notwithstanding, another explanation could be that selective participation and the opportunity for patients to refuse trial enrollment in the Lim et al study resulted in a more adherent population, and/or 1 that is more willing to become adherent.[32]

4.1 | Strengths and limitations

The study draws on the strengths of real-world evidence, use of PSM to successfully minimize important differences between groups and selection of a societal perspective to account for the wider economic burden to society.[14,28,38] Limitations include a small sample size and generalizability issues of our population at the tertiary hospital, although patients who meet indications for ULT in hospitals should not differ from those in primary care. Utilities and the WTP threshold are dependent on other populations in the absence of locally established values.[42] We have adjusted for group differences on nine patient variables that the literature considered critical for gout, but PSM as a methodology has its inherent constraints in the event where residual confounders are left unmeasured, or where known confounders are imprecisely measured. For example, sociodemographic and economic variables including education, marital status, income, and insurance status are unavailable in PASS. The effect of unmeasured covariates that do not reside within patient records—whether known and unknown from the literature—cannot be evaluated. There should be clear attempts in future observational studies to measure and control for differences in patient characteristics, including sociodemographics and disease status, to avoid dilution of effects.

5 | CONCLUSION

Through this study, considerable insight has been gained with regard to ULT adherence-enhancing interventions for long-term gout management. The cumulative results replicate reports of efficacy by Lim et al and provide robust evidence on its cost-effectiveness. To our knowledge, this is the first allopurinol adherence-enhancing intervention for which such an evidence base has been demonstrated and continued implementation of the program in routine clinical care is recommended. Its cost-effectiveness over the longer term should be evaluated.

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CONFLICT OF INTERESTS

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHOR CONTRIBUTIONS

All designated as authors have met the four criteria for authorship recommended by the International Committee of Medical Journal Editors (ICMJE).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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