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ORIGINAL ARTICLE

HEALTH CARE SCIENCE

Decision-making for early major amputation in selected diabetic foot ulcer patients with peripheral vascular disease

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Abstract

Objective: To estimate the costs from delaying major amputation in patients with concurrent diabetic foot ulcer and peripheral vascular disease. We seek to model economic benefits from saved costs from promoting timely major amputations among these patients.

Methods: Retrospective modeling using data from National University Hospital, Singapore. We identified patients who might have delayed major amputations by applying a hierarchical clustering algorithm. We then modeled the transitions of all patients over time with a Markov process using a number of relevant health states to enable estimation of cost outcomes. We next summarized the expected changes to the bed days used and cost outcomes arising from reassigning some patients who may have had a delayed amputation to timely amputation. The findings from the sample were scaled to reflect national incidence rates for this disease for the years 2014–2019 in Singapore.

Results and Conclusions: Nine of the 137 patients (6.57%) would be suitable for a major amputation at 3 months, yet in reality, their amputation was delayed. Based on this, and assuming a timely amputation is done for the entire population of patients in Singapore we expect annual savings of 264,791 bed days and $211 million in costs. These findings are preliminary and uncertain. The value of this paper is to show a method for estimating outcomes, report the findings from a small sample, and stimulate future research. New cohort studies might be designed to capture a wider range of outcomes and recruit a larger sample of individuals.

KEYWORDS
amputations, patients, costs

Abbreviations: A*STAR, Agency for Science, Technology and Research; DSRB, Domain Specific Review Board; IAF-PP, Industry Alignment Fund-Pre-Positioning Programme; IRB, Institutional Review Board; LightGBM, light gradient boosting machine; NHG, National Healthcare Group; WCIT, Wound Care Innovation for the Tropics; WIfI, wound, ischemia, and foot infection.

1 | INTRODUCTION

Diabetic foot ulcer is a complication of diabetes affecting 6.3% of the global population [1]. Current approaches to managing this problem include debridement, surgical revascularisation, minor amputation, or major amputation in the worst-case scenario [2]. In a patient with concurrent underlying peripheral vascular disease, the reduction in blood flow to the lower limb impedes wound healing, increasing the risk of infection and gangrene, as well as increasing the likelihood of amputation [3, 4]. While every effort is made to prevent limb loss, for some diabetic patients with multiple challenging conditions, amputation is inevitable.

Diabetes is associated with more severe manifestations of peripheral vascular disease such as chronic limb-threatening ischemia, particularly in more distal anatomical locations and involving more extensive calcified occlusions that make revascularisation challenging [2, 3, 5]. Diabetes is also associated with an increased rate of restenosis, especially in situations with reduced distal runoffs [5, 6]. Repeat ulcerations may also happen even after successful revascularisations [7].

Patients with concurrent diabetic foot ulcer and peripheral vascular disease will incur large healthcare costs. In Singapore, a country with comprehensive and accessible healthcare services and well-equipped vascular departments, a recent study revealed a minor amputation would cost US $10,468 and major amputation US $30,131 [8] and this is similar to other countries [9, 10]. In the United States, the annual direct healthcare cost of diabetic foot ulcer is comparable to the cost of cancer [11]. Diabetic foot ulcers are a substantial clinical and economic burden.

Limb salvage and reducing risk of death are the primary goals when managing diabetic chronic limb-threatening ischemia. Nonetheless, large costs might arise from repeat procedures or delays to unavoidable major amputations. While some patients will undergo a major amputation once it becomes evident that limb salvage is unlikely to succeed, others may delay or refuse the major amputation for reasons such as fear, social stigma, or perceived professional repercussions [12]. Indeed one study reported that patients with diabetic foot ulcer fear major amputations more than death [13]. This delay would in turn lead to increased healthcare costs from repeat minor procedures, further productivity losses from repeated hospitalizations, and possibly worse health-related quality of life from prolonged non-healing ulceration [14, 15]. It is plausible that hastening a patient's acceptance of a major amputation, when limb salvage is likely not possible would save healthcare resources and reduce an economic burden.

The aim of this study is to model the expected savings to healthcare costs from a situation where all patients who were deemed to require major amputation receive a timely amputation. We estimate the costs incurred from delaying major amputation for patients in whom a major amputation is inevitable. We seek to identify the possible economic benefits in terms of saved costs arising from promoting timely major amputations for these patients.

2 | METHODS

The data arose from a retrospective review of consecutive patients with critical limb ischemia presented to the National University Hospital, Singapore between November 1, 2015 and December 31, 2017. The data set contains 137 unique patients with below the knee peripheral vascular disease. Patients with a Rutherford score of 3 and below (claudication) were removed to obtain a more homogeneous data set. These patients have low risk of limb loss, compared to those with Rutherford score of 4 (ischemic rest pain) or above [16].

First, we organized the patients into three groups depending on “if” and “when” they received a major amputation above or below the knee: Group A had a major amputation by 3 months after initial admission to hospital and was deemed timely; Group B had major amputation between 3 and 12 months after initial admission to hospital; Group C had no major amputation at 12 months after initial admission to hospital, see Figure 1.

Second, we identify patients in Groups B and C who might have delayed inevitable amputations by applying a

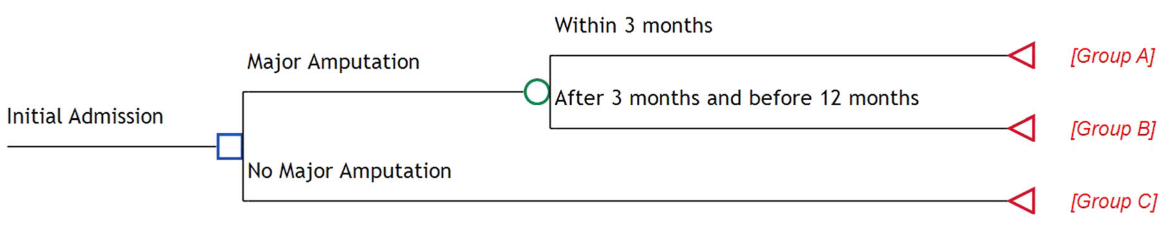

FIGURE 1 Competing outcomes within 12 months for patients after initial admission to hospital

hierarchical clustering algorithm [17] updated by information known to predict risks of major amputations. This information is available to clinical teams at the time of primary admission and so could be used as part of a prospective intervention. Clustering processes are better with fewer variables. Experts in wound care were asked to identify candidate variables likely to affect risks of major amputation and reported: age; gender; race; presence of hypertension; elevated lipids; recent stroke; Rutherford score; ischemic heart disease; number of patent arteries; wound location; diabetes; chronic kidney disease; wound infection; and, wound extent. The assessment of infection and wound extent was based on wound, ischemia, and foot infection (WIfI) classification [18]. Values for these variables updated a decision tree algorithm to enable a quantitative and readable interpretation of indicators for major amputation. A light gradient boosting machine (LightGBM) was used to determine the relative strength of the variables. An arbitrary threshold of 30 was used for the *F*-score and we made use of hierarchical clustering with Cosine similarity for a distance metric due to the presence of both one-hot encoded categorical variables and numerical variables. The expected outcome of this process is that some patients from Groups B and C who have similar risks of major amputation to those in group A can be reassigned to Group A. The size of Group A will therefore be expanded, and Groups B and C reduced.

Third is to model the transitions of all patients over time with a Markov process [19] using a number of relevant health states that include: no minor amputation, varying numbers of minor amputations, and major amputation, see Figure 2. This enables accurate estimation of cost outcomes based on the

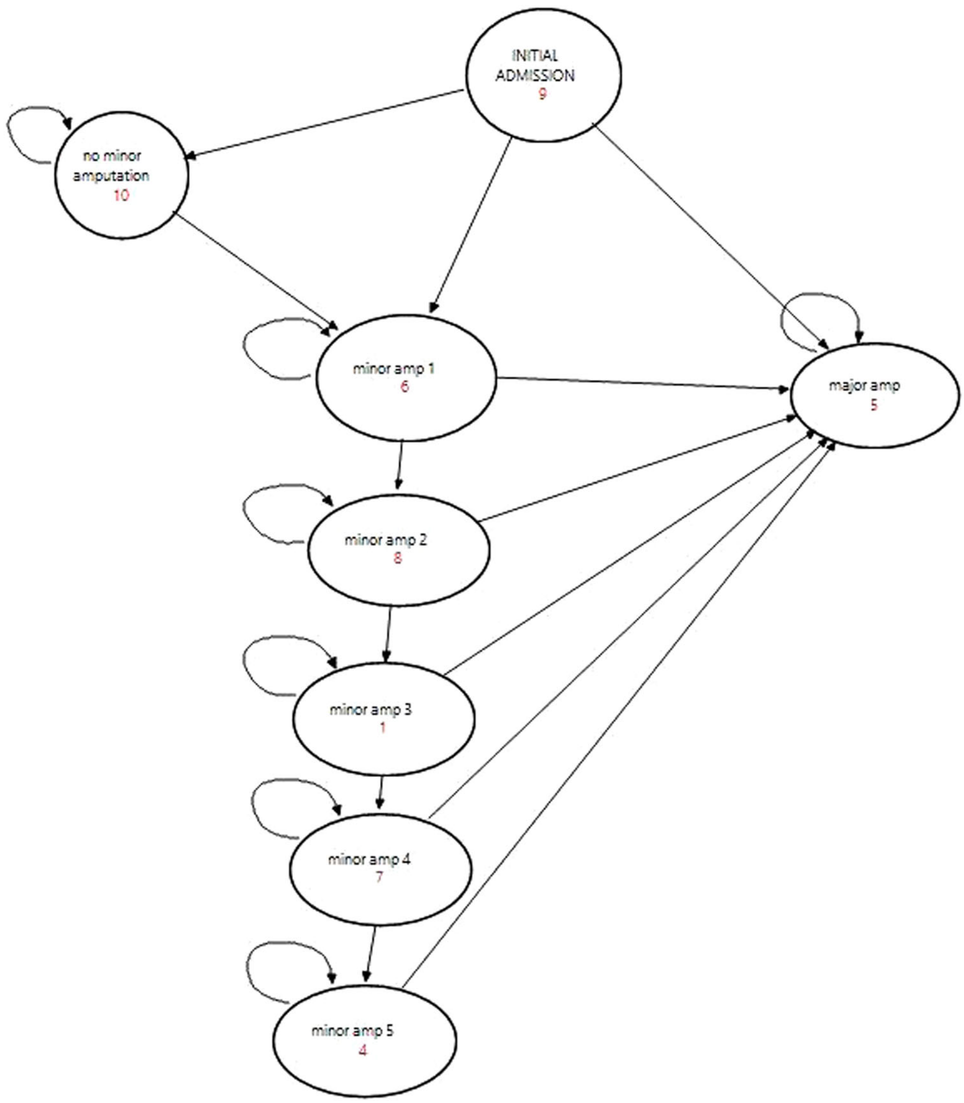

FIGURE 2 Markov model to show the healthcare events for all patients with peripheral vascular disease

treatments and provides a useful visualization of the services provided.

The transition probabilities were time-varying and specified with beta distributions. Random resamples from the prior distributions were used to generate 95% uncertainty intervals.

Fourth is to summarize the changes to the length of stay in hospital and cost outcomes arising from the reassignment of identified patients into Group A. The parameters for "length of stay" were fitted to a Gamma distribution using the method of moments [20]. The Gamma is bounded at zero and can accommodate negative skew found in lengths of stay data [21]. Random resamples from the prior distributions were used to generate 95% uncertainty intervals for length of stay and cost outcomes. We present the incremental change to length of stay in hospital and costs from a hypothetical decision to complete major amputation at 3 months for selected patients who have risks similar to those who currently have a major amputation at 3 months.

The final part of this analysis is to scale the estimated cost saving to reflect the national incidence rate for this disease for the years 2014 to 2019 in Singapore.

This study has been approved by the NHG Domain Specific Review Board (DSRB 2019/00917). Patient consent was not obtained as we use retrospective medical records that were fully anonymized before we gained access to them. The IRB committee waived the requirement for informed consent.

3 | RESULTS

Descriptive statistics are shown in Table 1 for all patients in the data set for the variables used in the hierarchical clustering algorithm.

Most of the cohort patients (79.6%) were in Group C where major amputation was not necessary. Two-thirds were male and approximately half are Chinese ethnicity. The risk factors for major amputation were also present among this sample. The LightGBM algorithm revealed "wound extent" and "age" as strong predictors, with "chronic kidney disease," "infection," and "number of patent arteries" as important with "lipids," "heart disease," and "gender" as less important, see Figure 3.

All relevant variables for risk factors were included in the clustering algorithm. The results of the hierarchical clustering process are shown by the dendrogram in Figure 4. The four clusters that emerged and shown in Table 2. Cluster 0 includes 56% of "Group A" patients and attracted five similar individuals from "Group B" and 17 similar individuals from "Group C." We interpret it is plausible that the "Group B" patients in Cluster 0 would be suitable for a major amputation at 3 months. We exclude the "Group C" patients from this because they reached 12 months without major amputation and so were unlikely to need one. There is little evidence from Clusters 1 and 2 that "Group B" patients would be suitable for major amputation at 3 months. The make-up of Cluster 3 suggests four individuals from "Group B" might be suitable for major amputation at 3 months.

We proceed with two competing versions of patients being reassigned to 3-month amputation. Option 1 is that based on Cluster 0, 5 former B individuals were modeled as having a major amputation at 3 months. Option 2 is that based on Clusters 0 and 3, an additional 4 former B individuals were modeled as having a major amputation at 3 months. Based on the reported incidences per 100,000 persons of peripheral vascular disease annually and a total population of 5.7 million, we estimate the number of annual incident cases, Table 3.

We show the membership of the Markov states for "existing practice" and "Options 1 and 2" using 2019 incident cases, see Appendix 1. This reveals large modeled increases in the use of major amputation for Options 1 and 2 respectively, and the 95% uncertainty intervals are shown.

For the comparison of cost outcomes from Options 1 and 2 to existing practice, the mean of the "lengths of stay" for the initial Group A patients is assigned to the new entrants from Group B. Due to the presence of large values that pull up the mean, we use a 30% trimmed mean to better estimate the length of stay of Group A patients. The cost of one hospital bed day in 2018 is based on $775 (95% CI: $770, $780) [22]. The impact on outcomes arising from the Options 1 and 2 compared to existing practice for all years are shown in Tables 4 and 5.

4 | DISCUSSION

Based on the findings from the model, some patients who demonstrated a delayed major amputation 4–12 months after initial treatment might be suitable for this procedure sooner. A different decision about when to do a major amputation could save resources and costs. The size of the modeled savings from Option 1 versus existing practice is large with an estimated 220,172 bed days released for the period 2014–2019. Given a mean length of stay of 4 days for regular inpatients, the real economic savings from a change of practice would be characterized by the health benefits gained from 55,043 additional admissions to acute care for no increase to the fixed costs of production [23]. When historic accounting costs were applied to a modeled bed day the monetary estimate of

TABLE 1 Descriptive statistics for peripheral vascular disease patients

	Group A	Group B	Group C	All patients
Total number	16	12	109	137
Demographics				
Male, *n* (%)	11 (68.8%)	10 (83.3%)	70 (64.2%)	91 (66.4%)
Race, *n* (%)				
Chinese	5 (31.2%)	8 (66.6%)	56 (51.1%)	69 (50.4%)
Malay	8 (50.0%)	2 (16.6%)	37 (33.9%)	47 (34.3%)
Indian	2 (12.5%)	0 (0.0%)	14 (12.8%)	16 (11.7%)
Others	1 (6.3%)	2 (0.16%)	2 (1.8%)	5 (3.6%)
Age, mean (SD)	61.13 (11.0)	61.92 (11.2)	64.27 (11.0)	63.81 (11.0)
Comorbidities				
Diabetes mellitus, *n* (%)	16 (100.0%)	12 (100.0%)	96 (88.1%)	124 (90.5%)
CKF/ESRF, *n* (%)	3 (18.7%)	2 (16.7%)	41 (37.6%)	46 (33.6%)
Chronic kidney failure	1 (6.3%)	1 (8.3%)	23 (21.1%)	25 (18.2%)
End-stage kidney failure	12 (75%)	9 (75.0%)	45 (41.3%)	66 (48.2%)
Ischemic heart disease, *n* (%)	10 (62.5%)	9 (75.0%)	61 (56.0%)	80 (58.4%)
Hyperlipidemia, *n* (%)	13 (81.3%)	8 (66.7%)	76 (69.7%)	97 (70.8%)
Hypertension, *n* (%)	14 (87.5%)	10 (83.3%)	87 (79.8%)	111 (81.0%)
Cerebral vascular accident, *n* (%)	0 (0.00%)	0 (0.0%)	14 (12.8%)	14 (10.2%)
Characteristics of wound				
Extent of wound, *n* (%)[a]				
No ulcer, no gangrene	0 (0.0%)	0 (0.0%)	8 (7.3%)	8 (5.8%)
Small ulcer	0 (0.0%)	1 (8.3%)	30 (27.5%)	31 (22.6%)
Gangrene limited to toes or deep ulcer	11 (68.8%)	7 (58.3%)	69 (63.3%)	87 (63.5%)
Extensive gangrene or extensive ulcer	5 (31.3%)	4 (33.3%)	2 (1.8%)	11 (8.0%)
Infection, *n* (%)[a]				
No infection	1 (31.7%)	2 (16.6%)	33 (30.2%)	36 (26.3%)
Mild infection	1 (14.4%)	1 (8.3%)	15 (13.8%)	17 (12.4%)
Moderate infection	2 (27.9%)	5 (41.2%)	32 (29.4%)	39 (28.5%)
Severe infection	12 (26.0%)	4 (33.3%)	29 (26.6%)	45 (32.8%)
Number of patent arteries, *n* (%)[b]				
0	10 (62.5%)	7 (58.3%)	62 (56.8%)	79 (57.7%)
1	6 (37.5%)	5 (41.7%)	34 (31.2%)	45 (32.8%)
2	0 (0.0%)	0 (0.0%)	10 (9.2%)	10 (7.3%)
3	0 (0.0%)	0 (0.0%)	3 (2.8%)	3 (2.2%)
Rutherford score, *n* (%)				
4 (ischemic rest pain)	0 (0.0%)	0 (0.0%)	6 (5.5%)	6 (4.3%)
5 (minor tissue lost)	14 (87.5%)	11 (91.7%)	85 (78.0%)	110 (80.3%)
6 (major tissue lost)	2 (12.5%)	1 (8.3%)	18 (16.5%)	21 (15.3%)

TABLE 1 (Continued)

	Group A	Group B	Group C	All patients
Wound location, *n* (%)				
No wound	0 (0.0%)	0 (0.0%)	8 (7.3%)	8 (5.8%)
Supramalleolar	0 (0.0%)	0 (0.0%)	8 (7.3%)	8 (5.8%)
Heel	2 (12.5%)	3 (25.0%)	8 (7.3%)	13 (9.5%)
Midfoot and toe	14 (87.5%)	9 (75.0%)	85 (78.0%)	108 (78.8%)
Length of stay in hospital, mean (SD)	42.6 (16.9)	81.2 (67.5)	46.0 (50.4)	48.7 (50.2)

[a]Assessment based on wound, ischemia, and foot infection (WIfI) classification.

[b]Among anterior tibial, posterior tibial, and peroneal artery.

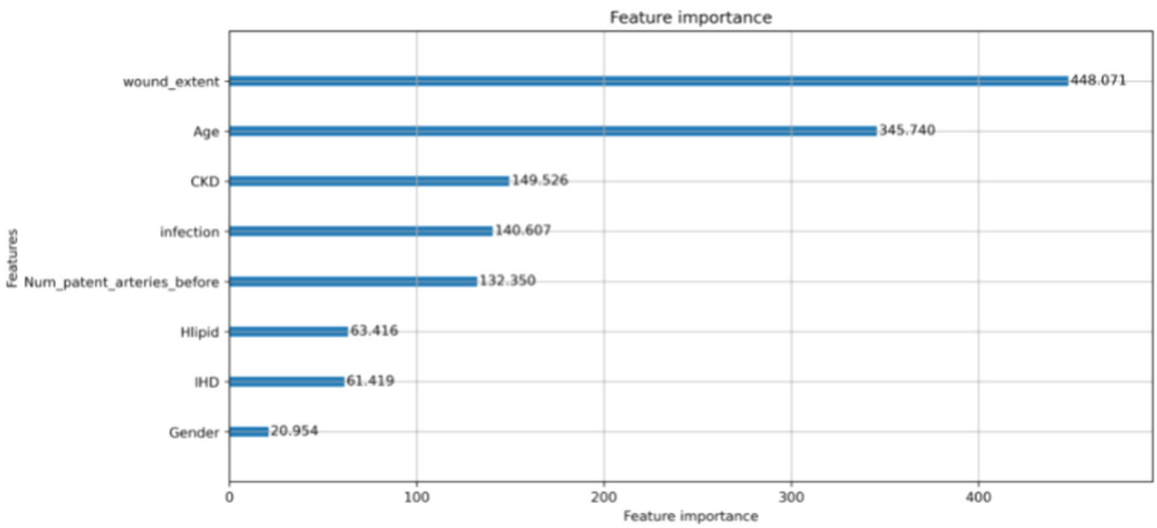

FIGURE 3 Feature Importance observed from LightGBM

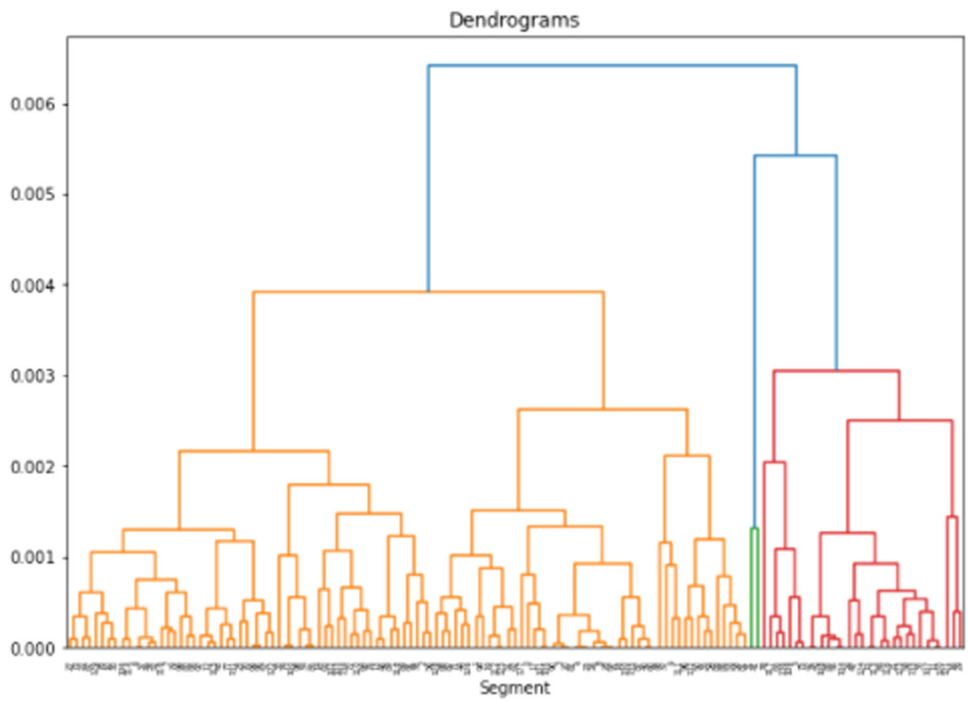

FIGURE 4 Results of the clustering algorithm shown as a dendrogram

costs savings for this time period was $171 M. Option 2 versus existing practice returns larger savings with 264,791 bed days saved and $211 M in costs avoided.

The threat to these conclusions is that inferences were drawn from very small samples and this study would need to be repeated on larger samples. Furthermore, the economic and healthcare cost of community care for diabetic foot ulcer patients with chronic limb-threatening ischemia incurred after hospital discharge were not captured. Studies of longitudinal data sets that follow these patients might be suitable for interrogation with these methods. We used severity of infection and number of patent arteries as candidate variables for the clustering algorithm, yet these may be not completely describe the risks of major amputation. Ideally, we would have used information on osteomyelitis occurrence, related pathogens, and use of antibiotics. In addition, data describing the degree of artery stenosis and calcification extent would have been useful. Finally, there would have been other costs related to nursing and amputation-related complication after discharge that could have been counted but no data were available.

We caution against using these results for a strong policy response. We see the value of this paper as showing methods that could be useful, pilot testing them with a small set of data, and then getting results that do shed light on an interesting hypothesis.

Key questions to be addressed with greater rigor are: whether clinicians could identify accurately which patient inevitably will require major amputation in the first 2–3 months of management; whether some patients and/or clinicians really delay an inevitable major amputation for reasons of fear, social stigma or perceived professional repercussions; whether patient's acceptance to major amputation can be moderated with information and education material; what would really be saved from shortening the time to major amputation for selected patients; whether patients health-related quality of life is

TABLE 2 Distribution of patients in each cluster

Cluster	Number of patients (% of total) A	B	C	Total
0	9 (56)	5 (42)	17 (16)	31
1	2 (13)	3 (25)	43 (39)	48
2	0 (0)	0 (0)	2 (2)	2
3	5 (31)	4 (33)	47 (43)	56
Total	16 (100)	12 (100)	109 (100)	137

TABLE 3 Annual incident cases of peripheral vascular disease

Year	Persons per 100,000 population	Annual rate	Incident cases
2014	265	0.265%	15,088
2015	264	0.264%	15,071
2016	250	0.250%	14,267
2017	280	0.280%	15,949
2018	301	0.301%	17,134
2019	294	0.294%	16,735

TABLE 4 Modeled change to key outcomes from existing practice versus Option 1

Option 1 versus existing practice				
	Mean (95% interval)			
Year	Number of bed days	Costs	Number of minor amputations	Number of major amputations
2014	−35,218 (−37,443, −32,993)	−$27,271,433 (−$28,995,036, −$25,547,830)	−282 (−1332, 768)	85 (−16, 186)
2015	−35,999 (−38,442, −33,556)	−$27,879,232 (−$29,771,454, −$25,987,011)	−459 (−678, −42)	32 (−42, 106)
2016	−32,783 (−34,656, −30,910)	−$25,385,155 (−$26,835,665, −$23,934,645)	−142 (−850, 365)	−39 (−102, 24)
2017	−38,380 (−40,404, −36,356)	−$29,727,271 (−$31,294,409, −$28,160,134)	−266 (−766, 366)	14 (−130, 158)
2018	−39,470 (−42,050, −36,890)	−$30,576,584 (−$32,574,317, −$28,578,851)	−316 (−511, −195)	−92 (−189, 5)
2019	−38,322 (−40,728, −35,917)	−$29,681,883 (−$31,543,548, −$27,820,218)	−513 (−947, −79)	−2 (−67, 63)

TABLE 5 Modeled change to key outcomes from existing practice versus Option 2

Option 2 versus existing practice				
	Mean (95% interval)			
Year	Number of bed days	Costs	Number of minor	Number of major
2014	−42,077 (−44,304, −39,850)	−$32,586,204 (−$34,312,810, −$30,859,598)	1535 (700, 2370)	134 (−152, 420)
2015	−45,138 (−47,373, −42,903)	−$34,963,134 (−$36,695,785, −$33,230,483)	1305 (1150, 1460)	12 (−62, 86)
2016	−34,382 (−36,244, −32,521)	−$32,414,164 (−$34,106,574, −$30,721,754)	639 (164, 1114)	−122 (−202, 446)
2017	−45,283 (−47,466, −43,099)	−$35,072,433 (−$36,764,541, −$33,380,324)	350 (141, 459)	7 (−130, 144)
2018	−49,745 (−52,043, −47,447)	−$38,536,732 (−$40,314,779, −$36,758,685)	618 (515, 721)	−72 (−252, 108)

improved in the medium to long term from timely amputation; and, whether an intervention could be designed and implemented and how effective and costly it might be.

If these questions could be addressed with a combined effort from qualitative researchers and quantitative approaches, there could be good opportunity to improve the performance of health services and improve the quality of care for an important patient group.

AUTHOR CONTRIBUTIONS

Lim York Tee Gorden: Conceptualization (supporting); Data curation (lead); Formal analysis (lead); Funding acquisition (supporting); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Ying Fangting Ariel**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal); Writing – review & editing (equal). **Ho Pei**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal); Writing – review & editing (equal). **Lingyan Meng**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal); Writing – review & editing (equal). **N. G. Yi Zhen**: Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Project administration (lead); Writing – original draft (equal); Writing – review & editing (equal). **Nicholas Graves**: Conceptualization (lead); Data curation (equal); Formal analysis (equal); Funding acquisition (lead); Investigation (lead); Methodology (lead); Project administration (equal); Writing – original draft (lead); Writing – review & editing (lead).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

This study has been approved by the NHG Domain Specific Review Board (DSRB 2019/00917). Patient consent was not obtained as we use retrospective medical records that were fully anonymized before we gained access to them. The IRB committee waived the requirement for informed consent.

INFORMED CONSENT

None.

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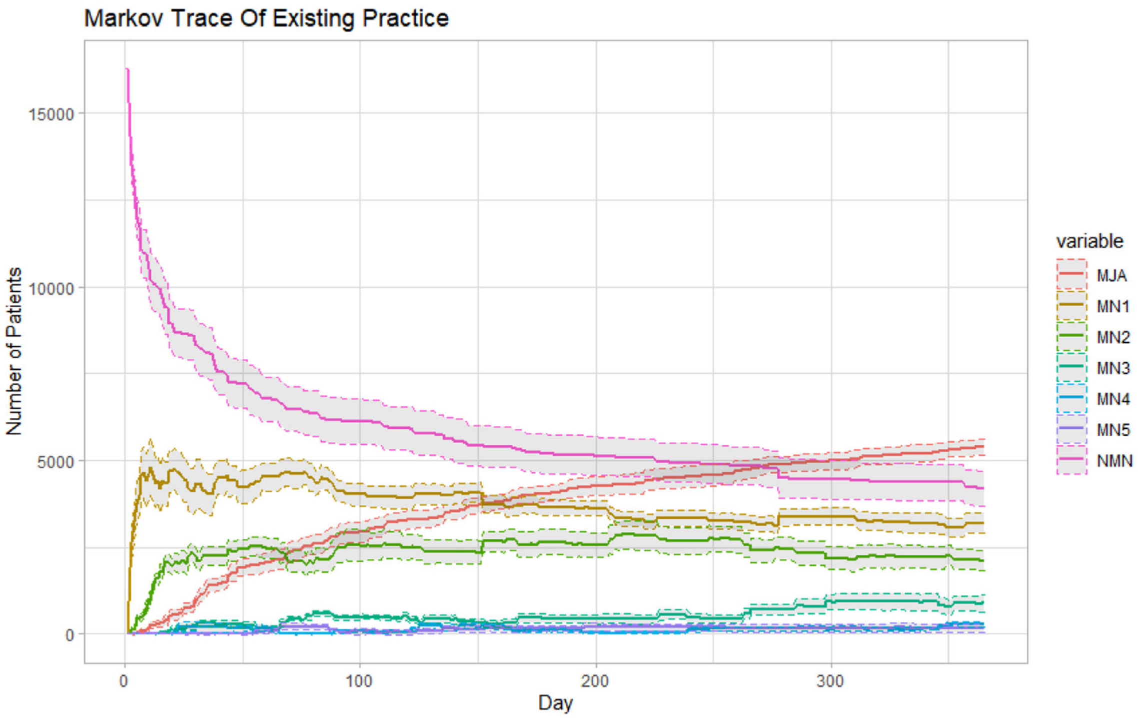
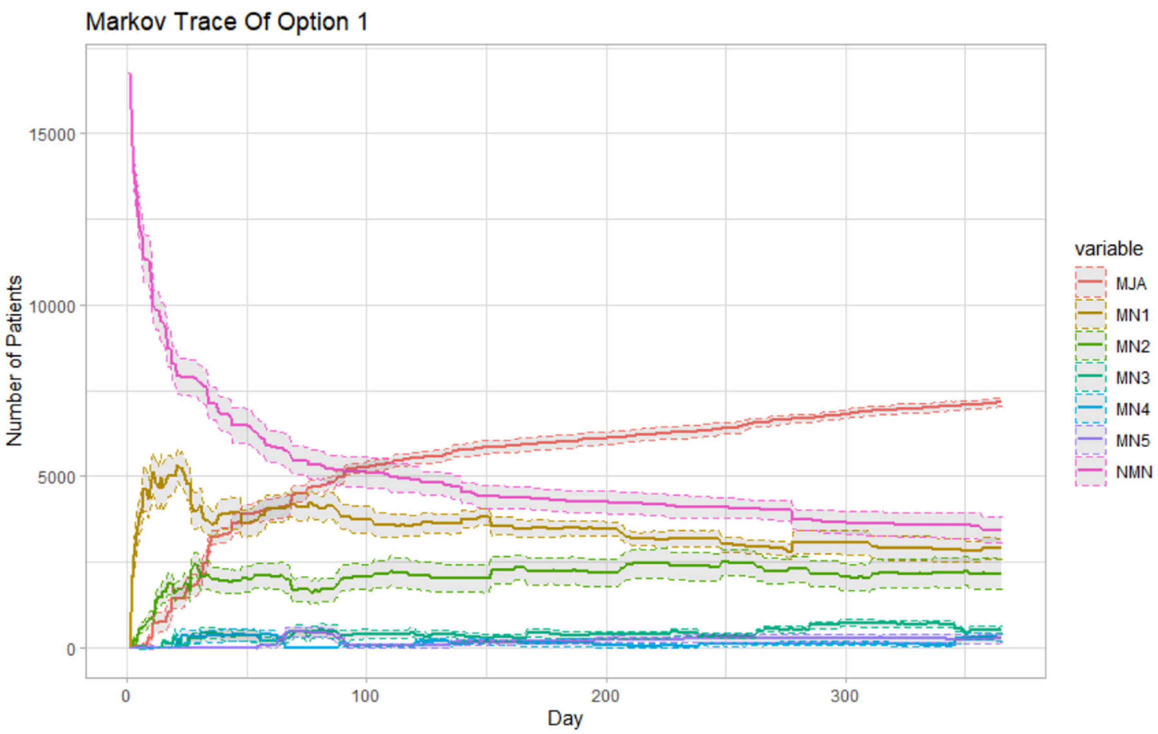
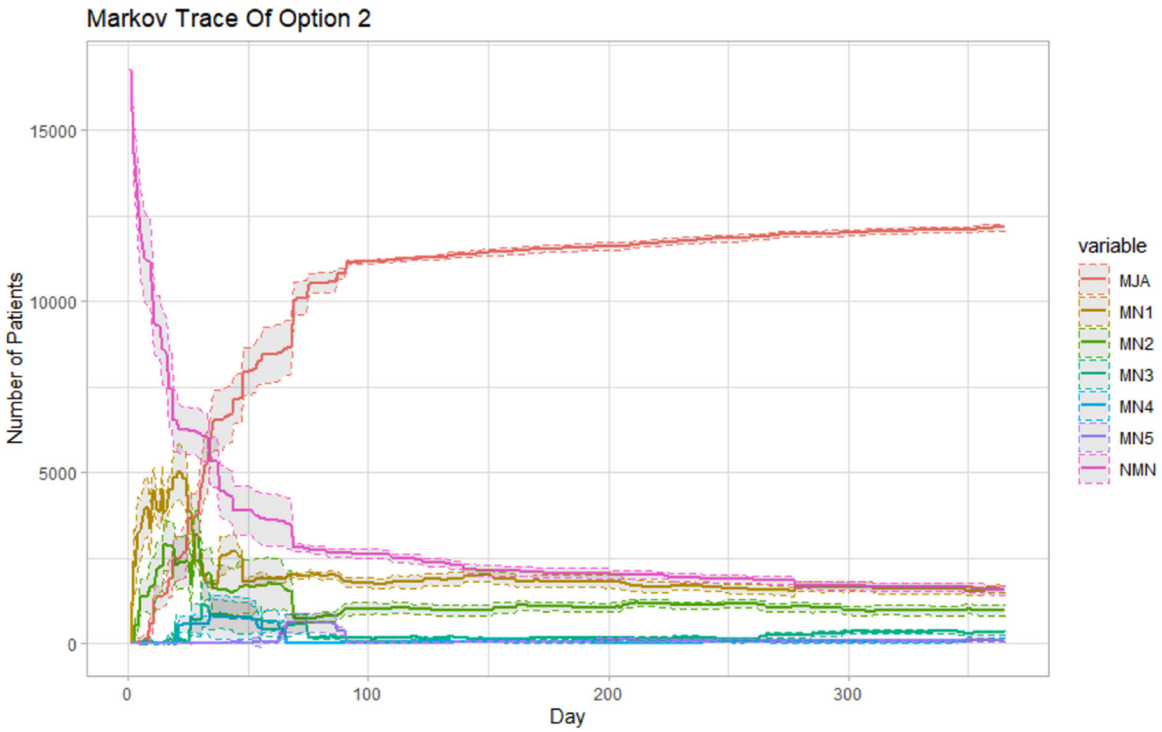
APPENDIX 1: MEMBERSHIP OF THESE MARKOV STATES FOR THE 1000 MODELLED INDIVIDUALS.







MJA = Major amputation

MN1 to MN5 = first for fifth minor amputations

NMN = no major amputations