Evaluation of the Clinical and Economic Burden of Diabetic Foot Ulcers in Singapore and Outcome Improvement through Health Systems Innovations

Lo Zhiwen (Joseph)

Lee Kong Chian School of Medicine

2023

Evaluation of the clinical and economic burden of diabetic foot ulcers in Singapore and outcome improvement through health systems innovations

Name: Lo Zhiwen (Joseph)
Programme: [188] Ph.D. (LKCMEDICINE)

A thesis submitted to the Nanyang Technological University in partial fulfilment of the requirement for the degree of Doctor of Philosophy

2023

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research, is free of plagiarized materials, and has not been submitted for a higher degree to any other University or Institution.

20/08/2023	
Date	Lo Zhiwen (Joseph)

Supervisor Declaration Statement

I have reviewed the content and presentation style of this thesis and declare it is free of plagiarism and of sufficient grammatical clarity to be examined. To the best of my knowledge, the research and writing are those of the candidate except as acknowledged in the Author Attribution Statement. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

20/08/2023

Date

Josip Car (Supervisor)

Professor of Digital Health Sciences
Centre for Population Health Sciences
Lee Kong Chian School of Medicine
Nanyang Technological University

20/08/2023

Date

Keith Harding (Co-Supervisor)

Professor Emeritus
Cardiff University, United Kingdom

Authorship Attribution Statement

This thesis contains material from five papers published in the following peer-reviewed journals, where I was the first and corresponding author.

1. Chapter 2 was published by **Lo ZJ**, Surendra NK, Saxena A, Car J. Clinical and economic burden of diabetic foot ulcers: A 5-year longitudinal multiethnic cohort study from the tropics. Int Wound J. 2021; 18(3):375-386
    - I designed the study, performed the study, and prepared the manuscript.
    - Surendra NK assisted with statistical analysis and reviewed the manuscript.
    - Saxena A reviewed the statistical analysis and manuscript.
    - Car J provided supervision and reviewed the manuscript.
2. Chapter 3 was published by **Lo ZJ**, Chandrasekar S, Yong E, et al. Clinical and economic outcomes of a multidisciplinary team approach in a lower extremity amputation prevention program for diabetic foot ulcer care in an Asian population: A case–control study. Int Wound J. 2022; 19(4):765-773
    - I designed the study, performed the study, and prepared the manuscript.
    - Chandrasekar S, Yong E, and Liew H co-designed the study and reviewed the manuscript.
    - Hong Q, Zhang L, Chong LRC, Tan G, Chew T, Sani NF, Cheong KY, Cheng LRQ, Tan AHM, Muthuveerappa S, Lai TP, Goh CC, Hoi WH, Lin JHX, Chew DEK, Lim B, and Yeo PS are clinical collaborators who reviewed the manuscript.
    - Chan YM and Koo HY are research coordinators who assisted with recruitment and data management.
    - Ang GY and Zhu Z assisted with statistical analysis and reviewed the manuscript.
3. Chapters 4 and 5 were published by **Lo ZJ**, Tan E, Chandrasekar S, et al. Diabetic foot in primary and tertiary (DEFINITE) Care: A health services innovation in coordination of diabetic foot ulcer (DFU) Care within a healthcare cluster - 18-month results from an observational population health cohort study. Int Wound J. 2023; 20(5):1609-1621
    - I designed the study, performed the study, and prepared the manuscript.
    - Tan E, Chandrasekar S, Ooi D, and Liew H co-designed the study and reviewed the manuscript.
    - Ang G assisted with statistical analysis and reviewed the manuscript.

- Yong E, Hong Q, Chew T, Farhan MFM, Zhu X, Ang P, Law C, Raman N, Park D, Tavintharan S, Hoi WH, and Lin J are clinical collaborators who reviewed the manuscript.
- Koo HY, Choo J, Low KQ, and Low R are executives who assisted with recruitment and data management.
- Venkataraman K, Car J, and Chew DEK provided supervision and reviewed the manuscript.

4. Chapter 11 was published by **Lo ZJ**, Chong B, Tan E, et al. Patients, carers and health care professionals' perspectives on a patient-owned surveillance system for diabetic foot ulcer care: A Qualitative Study. Digit Health. 2023. Jun 21:9:20552076231183544
   - I designed the study, performed the study (including interviews), and prepared the manuscript.
   - Chong B assisted with manuscript revisions.
   - Tan E, Ooi D, Liew H, Hoi WH, and Wu K are clinical collaborators who reviewed the manuscript.
   - Cho YT, Surendra NK, Mammadova M, Nah A, and Goh V assisted with interviews and data management.
   - Car J provided supervision and reviewed the manuscript.
5. Chapter 12 was published by **Lo ZJ**, Harish KB, Tan E, et al. A feasibility study on the efficacy of a patient-owned wound surveillance system for diabetic foot ulcer care (ePOWS study). Digit Health. 2023. Oct 6:9:20552076231205747
   - I designed the study, performed the study and prepared the manuscript.
   - Harish KB assisted with manuscript revisions.
   - Tan E, Zhu J, Chan S, Liew H, Hoi WH and Wu K are clinical collaborators who reviewed the manuscript.
   - Liang S, Cho YT and Koo HY assisted with study and data management.
   - Car J provided supervision and reviewed the manuscript.

20/08/2023

Date

Lo Zhiwen (Joseph)

During the Ph.D. period, I have also coauthored these ten related publications, which are referenced in the thesis:

1. **Lo ZJ**, Lim X, Eng D, Car J, Hong Q, Yong E, Zhang L, Chandrasekar, Tan GWL, Chan YM, Sim SC, Oei CW, Zhang X, Dharmawan A, Ng YZ, Harding K, Upton Z, Yap CW, Heng BH. Clinical and economic burden of wound care in the tropics: a 5-year institutional population health review. Int Wound J 2020; 17:790-803.
2. Chan KS, **Lo ZJ**. Wound assessment, imaging and monitoring systems in diabetic foot ulcers: a systematic review. Int Wound J 2020; 1-15
3. Natesan S, Li JY, Kyaw KK, et al, **Lo ZJ**. Effectiveness of comanagement model: geriatric medicine and vascular surgery. J Am Med Dir Assoc. 2022;23(4):666-670.
4. Chan KS, Chan YM, Tan AHM, Liang S, Cho YT, Hong Q, Yong E, Chong LRC, Zhang L, Tan GWL, **Lo ZJ**. Clinical validation of an artificial intelligence-enabled wound imaging mobile application in diabetic foot ulcers. Int Wound J 2022; 19: 114-124
5. Riandini T, Pang D, Toh MPHS, Tan CS, Choong AMTL, **Lo ZJ**, Chandrasekar S, Tai ES, Tan KB, Venkataraman K. National rates of lower extremity amputations in people with and without diabetes in a multiethnic Asian population: a ten-year study in Singapore. Eur J Vasc Endovasc Surg 2022; 63: 147-155
6. Yong E, Gong H, Liew H, Chan YM, Neo S, Pan Y, Pua U, **Lo ZJ**, Zhang L, Mak M, Chong L, Hong Q, Tan GWL, Chua MJ, Mohd Fadil MFB, Chandrasekar S. Getting a foothold on diabetic foot disease – outcomes of a multidisciplinary clinical pathway for inpatient diabetic foot care: a 17-year institutional review. Int J of Lower Extremity Wounds. 2023 Jun 27;15347346231183740.
7. Graves N, Ganesan G, Tan KB, Goh OQM, Ho J, Chong TT, Bishnoi P, Carmody D, Ang SY, Ng YZ, **Lo ZJ**, Yong E, Aloweni FAB, Wang Z, Harding K. Chronic wounds in a multiethnic Asian population: a cost of illness study. BMJ Open 2023; 13:e065692
8. **Lo ZJ**, Mak MHW, Liang S, Chan YM, Goh CC, Lai T, Tan A, Thng P, Rodriguez J, Weyde T, Smit S. Development of an explainable artificial intelligence model for Asian vascular wound images. Int Wound J 2023; 1-14 doi:10.1111/iwj.14565
9. Ng GWY, Gan KF, Liew H, et al, **Lo ZJ**. A Systematic Review and Classification of Factors Influencing Diabetic Foot Ulcer Treatment Adherence, in Accordance with the WHO Dimensions of Adherence to Long-Term Therapies. Int J of Lower Extremity Wounds. 2024. Doi:10.1177/15347346241233962

10. Ge L, Zhao J, Tan M, et al, **Lo ZJ**. Multi-disciplinary diabetic limb salvage programme in octogenarians with diabetic foot ulcers is not futile: An observational study with historical controls. Int Wound J. 2024. Doi:10.1111/iwj.14801

20/08/2023

Date

Lo Zhiwen (Joseph)

Acknowledgments

- I sincerely thank my PhD Supervisor Professor Josip Car and Co-Supervisor Professor Keith Harding for their inspiration, guidance, and mentorship throughout these 4 years
- Thesis Advisory Committee: Professor Maurice van Steensel (chair), Professor David Becker and A/Professor Steven Thng
- Qualifying Examiners: Professor Helen Smith (chair), Professor David Becker, A/Professor Tan Ern Yu
- Professor Shervanthi Homer-Vanniasinkam, for encouraging me to embark on this journey more than 4 years ago
- Woodlands Health Department of Surgery: Dr Chua Wei Chong, Dr Sadhana Chandrasekar, Dr Shaun Chan, Dr Pravin Lingam and Dr Lee Chee Wei
- Woodlands Health research colleagues – Ms Kate Siah, Ms Juliana Zheng, Ms Liang Shanying, Ms Cho Yuan Teng
- National Healthcare Group research colleague – Ms Heiny Tan
- NHG DM Foot Workgroup and DEFINITE Care – Dr Elaine Tan, Dr Desmond Ooi, Dr Liew Huiling, Dr Yong Enming, Dr Hong Qiantai, Ms Tiffany Chew, Sis Julia Zhu, Ms Chelsea Law, Dr Hoi Wai Han, Dr Jaime Lin, Ms Koo Hui Yan, Ms Julia Choo, Mr Low Kai Qiang, Ms Deborah Lim, Ms Tan Cin Yee, and Dr Daniel Chew
- NHG Health Services and Outcomes Research colleagues – Dr Gary Ang, Dr Ge Lixia, Dr Sun Yan, Dr Joseph Molina
- Family and loved ones – my wife (Jia Hui) and daughters (Joy and Grace), for your unwavering support and longsuffering
- All my patients – who taught me so much through their life experiences
- My faith and everlasting hope in my Lord and Savior Jesus Christ, who said in Mark 2:17 "They that are whole have no need of the physician, but they that are sick: I came not to call the righteous, but sinners to repentance"

To God be the glory

Psalm 121 (verses 1 to 3)

I will lift up mine eyes unto the hills, from whence cometh my help.

My help cometh from the LORD, which made heaven and earth.

He will not suffer thy foot to be moved: he that keepeth thee will not slumber.

Table of Contents

Thesis Summary

This mixed-methods research aims to evaluate the burden of diabetic foot ulcer (DFU) disease in Singapore and improve outcomes through health systems innovation of coordinated multi-disciplinary team (MDT) care between primary and tertiary care. Our approach involved retrospective observational studies across hospital and healthcare clusters, evaluating DFU incidence, associated amputation rates, metabolic control and direct healthcare costs. Furthermore, we qualitatively identified care gaps and optimized guidelines-based MDT care between primary and tertiary care using a prospective healthcare cluster-wide health systems innovation. We conducted a quantitative evaluation of the outcomes of the prospective treatment cohort (2020–2022, *n*=4,660) and propensity score matched (PSM) against a control group (2016–2017, *n*=5,462). Our findings revealed a heavy clinical and economic burden of DFU disease in Singapore. We demonstrated a significant improvement in amputation-free survival, metabolic control and direct healthcare cost savings by implementing a health systems innovation of coordinated MDT care between primary and tertiary care. In addition, we demonstrated the feasibility and potential benefits of a patient-owned digital health application for DFU monitoring, using both qualitative and quantitative approaches.

(Summary word count: 177 words)

(Total thesis word count: 38,399 words, excluding references and appendices)

Chapter 1: Introduction and Research Questions

There is a global epidemic of diabetes mellitus (DM), with an estimated 537 million adults worldwide living with this disease (10% of adults) [1]. Chronic complications of DM include atherosclerotic cardiovascular diseases, which may result in peripheral arterial disease (PAD) and peripheral neuropathy (e.g., motor, sensory, or autonomic dysfunction). These complications can contribute to the development of DFUs [2-3]. Notably, approximately 18.6 million patients with DM develop DFU annually (3.5% annual incidence among patients with DM) [4]. In 2015, the global prevalence of patients with DFUs was estimated as 9.1–26.1 million, accounting for almost 5% of adults with diabetes [1]. The lifetime risk of a patient with DM developing a DFU is approximately 19%–34% [5].

For patients with DFU in Europe, more than 50% of wounds become infected [6]. In addition, up to 20% of patients with moderate-to-severe infections eventually require minor (i.e., toes or part of the foot or distal to the ankle) or major (i.e., above the ankle) lower extremity amputations (LEAs) [7]. Approximately 20% of patients with DFUs require hospitalization [8] because the existence of DFUs and their associated infections constitute a significant risk factor for emergency department (ED) visits and hospital admissions among patients with DM in the United States (US) [9]. Likewise, in the United Kingdom (UK), diabetic foot problems are the most frequent cause of DM-related hospital admissions [10]. Globally, an estimated 1.6 million LEA are attributed to DFU annually [11], with DM-related LEA incidences ranging from 78 to 704 per 100,000 person-years [12]. However, owing to disparities in healthcare access worldwide and across socioeconomic strata, there is a resultant inequity in diabetes-related lower extremity complications (DRLEC) across geography, communities, and ethnicities [13-14].

In UK, the 5-year risk of death for a patient with DFU is approximately 2.5 times higher than that for a patient with DM but without DFU [15]. A meta-analysis of patients with DM reported a crude rate of 231 deaths per 1,000 patient-years in patients with DFUs *versus* 182 deaths per 1,000 patient-years in patients without DFUs [16]. The estimated 5-year mortality rate for patients with DFU is 30%, which increases to more than 70% for patients with major LEA. This is comparable to an all-reported cancer 5-year mortality rate of 31% [17]. Data from Texas (US), showed that patients with coexisting end-stage renal failure (ESRF) have an even higher mortality risk of 74% at 2 years [18]. In Norway, the risk of death at 10 years for a patient with DFU is double that of a patient with DM but without DFU [19]. Current literature does not reveal whether such a high mortality rate results from a combination of comorbidities, lack of activity, and deconditioning after LEA or other factors [2-3].

Nonetheless, besides the increased healthcare utilization and mortality risks for patients with DFU, a significant decrease is noted in their physical function and health-related quality of life (HRQOL) [20], with almost 50% of patients reporting symptoms of depression [21]. In the Eurodiale study involving 1,232 patients presenting with new DFUs, patients reported poor overall HRQOL, with problems primarily in the mobility and pain/discomfort domains [22]. Patients with active DFU reported poorer HRQOL than those who underwent successful minor LEA. However, there is a paucity of quality data on HRQOL outcomes for DM-related LEA [23].

Consequently, diabetic foot disease carries a heavy economic burden. In the US, US$176 billion is spent annually on direct costs for diabetes care, with approximately one-third of this expenditure related to DRLEC [24]. The direct healthcare cost of DFU treatment in the

US was roughly US$9–$13 billion annually during 2007–2010 [25]. In UK, the estimated economic burden of diabetic foot disease amounted to US$1.4–$1.6 billion, almost 1% of the health service budget [26]. This rising economic burden posed by diabetic foot disease is also noted in numerous other health economies worldwide, with substantial associated indirect societal costs, such as the loss of individual earnings, the burden to carers, and the effects of absenteeism on employers [27-28]. This situation is further worsened by the reported DFU recurrence rates of 40% within 1 year, 60% within 3 years, and 65% within 5 years after healing [2]. Therefore, for patients with DFU wound closure, it may be more helpful to consider a state of remission rather than healing. Like cancer, the concept of remission offers a more effective framework for allocating resources, organizing care, and communicating information about risks [29].

Owing to the complexity of diabetic foot disease management, the International Working Group for Diabetic Foot Guidelines (IWGDF) recommends an MDT approach in the care of patients with DFU [30], which reduces DM-related LEA [31]. Although the team composition and activities of an MDT can vary across institutions, it generally includes at least one medical specialty clinician (most commonly endocrinology, infectious diseases, or primary care) and two or more surgical specialty clinicians (vascular, podiatry, orthopedics, or plastic surgery) [32]. The MDT should address six aspects of care: wound, microbiology, biomechanics with appropriate footwear, foot circulation, metabolic control, and patient education [33]. In addition, expertise in the prescription and management of custom-made offloading therapeutic footwear is recommended [34-35], along with suggestions to include clinicians with expertise in rehabilitation, nutrition, and psychological care [3, 21]. Although an MDT approach to aggressive limb preservation for patients with DFUs may increase direct healthcare costs in the short term, improved screening with prevention programs and expedited referral workflows that facilitate timely access to limb salvage procedures may offset the costs of implementing diabetic foot teams over the long term by improved access to care and reduction in DRLEC [36].

In Singapore, the prevalence of DM has increased from 8.2% in 2004 to 11.3% in 2010, with a further projected increase to 15% in 2050 [37]. Between 2008 and 2013, estimates indicate that the rate of all DM-related LEA has increased from 11.0/100,000 population to 13.3/100,000 population [38]. Although this mirrors the worldwide rising trend of DM-related LEA, Singapore has faced unfavorable outcomes compared to other Organization for Economic Cooperation and Development (OECD) countries. In 2021, Singapore's DM-related major LEA rate of 12.1/100,000 population was almost twice the OECD average of 6.4/100,000 population [39]. Despite the "War on Diabetes" declared by the Singapore Ministry of Health in 2016 to rally a whole-of-nation effort to tackle diabetes and its complications [40], contemporary data on the clinical and economic burden of diabetic foot disease in Singapore, coupled with health services interventions to target the management of patients with DFUs are severely lacking. Hence, this project aims to evaluate the clinical and economic burden of DFU in Singapore and improve outcomes through health systems innovation of coordinated MDT care between primary and tertiary care.

Research Question 1: What is the clinical and economic burden of DFU in Singapore?

- This will be addressed in Chapter 2: Evaluation of the Clinical and Economic Burden of DFU at the Hospital (2013–2017) and Public Healthcare Cluster (2016–2017) Levels

Research Question 2: How to improve outcomes of patients with DFUs through coordinated MDT care between primary and tertiary care?

- This will be addressed in Chapter 3: Evaluation of the Clinical and Economic Outcomes of an MDT Approach in a LEAPP Clinic for DFU Care ; Chapter 4: Mixed-Methods Evaluation on Care Gaps for DFU Care at the Healthcare Cluster Level with Resultant Health Systems Innovation Methodology to DEFINITE Care

Research Question 3: With coordinated MDT care between primary and tertiary care, what are the clinical and economic outcomes for patients with DFU?

- This will be addressed in Chapter 5: DEFINITE Care Cohort (2020–2022) ; Chapter 6: Propensity Score Matching and Analysis of DEFINITE Care (2020–2022) *Versus* Control (2016–2017) ; Chapter 7: DEFINITE Subgroup Analysis: Characteristics and Outcomes of Patients Managed by MDT LEAPP Clinic

Research Question 4: What are the characteristics and outcomes for at-risk subgroup populations?

- This will be addressed in Chapter 8: DEFINITE Subgroup Analysis: Characteristics and Outcomes of Patients Who Defaulted on Clinic Follow-ups ; Chapter 9: DEFINITE Subgroup Analysis: Characteristics and Outcomes of Octogenarians With DFUs ; Chapter 10: DEFINITE Subgroup Analysis: Characteristics and Outcomes According to Primary Care Catchment Population

Research Question 5: **How can we leverage on technology and digital health in our care for patients with DFU?**

- This will be addressed in Chapter 11: Digital Health: A Qualitative Study on Patients, Carers, and Healthcare Providers' Perspectives on a Patient-Owned Surveillance System for DFU Care ; Chapter 12: Digital Health: Feasibility Study on the Efficacy of a Patient-Owned Wound Surveillance System for DFU Care

Chapter 2: Evaluation of the Clinical and Economic Burden of DFU at the Hospital (2013–2017) and Public Healthcare Cluster (2016–2017) Levels

Summary

We conducted a 5-year (2013–2017) longitudinal multi-ethnic cohort study at a university tertiary hospital in Singapore and at our public healthcare cluster (2016–2017) to evaluate the clinical and economic burden of patients with DFU. The findings of both analyses revealed a significant clinical and economic burden of DFU. Most patients were elderly males with a higher likelihood of Malay and Indian ethnicities. They demonstrated significant comorbidities of hypertension, dyslipidemia, ischemic heart disease (IHD), chronic kidney disease (CKD), and poor diabetes control. At 1 year follow-up, the minor LEA rate was 1 in 3 patients, the major LEA rate was more than 1 in 20 patients, and the mortality rate was almost 1 in 3 patients, with heavy healthcare utilization and mean direct healthcare cost per patient just under US$12,000 (SG$16,000) per year. Data from this analysis are employed as the control cohort for propensity-score matching (PSM) in Chapters 6–11.

Methodology

Clinical management and journey for a patient with DFU within the historical cohort

Typically, a patient with DFU presents to the hospital *via* the hospital's specialist outpatient clinic (SOC) or emergency department (ED) and receives subsequent treatments in inpatient or outpatient care settings. Patients were eligible for inclusion in the study if they had ≥1 SOC visit or ≥1 inpatient episode. Only SOC visits and inpatient episodes related to DFU treatments were considered, including DFU-related admissions such as surgical debridement, minor or major LEA, antibiotic therapy, or revascularization. Lower extremity "minor amputation" was defined in the literature as amputations distal to the ankle (e.g., toe or foot amputations). Lower extremity "major amputation" was defined as amputation proximal to the ankle (e.g., below-knee transtibial amputation [BKA] or above-knee transfemoral amputation [AKA]). In addition, the analysis encompassed DFU-related SOC visits to podiatry, wound nurses, vascular surgery, orthopedic surgery, or endocrinology. Patient age, sex, race, wound anatomy, comorbidities, and clinical and biochemical markers present on the date of index DFU diagnosis were reported.

Analysis methodology at the hospital level (2013–2017)

First, we performed a longitudinal cohort analysis of inpatient and outpatient electronic medical record (EMR) databases from January 2013 to December 2017 in a 1,700-bed university tertiary hospital in Singapore. Within Singapore's public healthcare system, all medical records are digitized within the EMR database, which forms an accurate data source for both clinical and direct healthcare cost. The Health Services Outcomes Research unit retrieved clinical, administrative, and healthcare cost data from the Population Health Registry using the diagnosis, surgical procedure, and service codes of the International Classification of

Diseases (ICD9 and ICD10) (Appendix 1). Subsequently, these data were matched with an institutional wound-specific EMR system (eWounds), which contained more than 500,000 wound-related entries during 2013–2017. The aim was to ensure a corresponding International Classification of Diseases (ICD) diagnosis of DFU with an actual documented wound. Direct healthcare costs were calculated from a patient's perspective (before government subsidies), including physician fees, inpatient hospital stays, procedures, supportive dressings, and adjuvant therapy. Singapore's healthcare system adopted a mixed financing system, whereby healthcare subsidies were derived from nationalized life insurance schemes and deductions from the compulsory savings plan *via* the Central Provident Fund [41].

Health service utilization at the hospital level (2013–2017)

The incidence of hospitalizations (including length of stay [LOS)), ED visits, SOC visits, and surgeries attributable to DFU were filtered from the Population Health Registry based on above-mentioned ICD codes and the presence of wounds, corroborating with clinical expert guidance and patient pathways. For example, admissions for LEA or surgical debridement of the foot were considered relevant to DFU. However, admissions for arteriovenous fistula creation or coronary artery bypass were considered unrelated. Concerning surgical SOC visits, only visits to vascular surgery, orthopedic surgery, and podiatry were included. The gross amount charged per visit, admission, or both and its related procedures were retrieved from the Population Health Registry for cost calculations. The evaluated economic outcomes include total healthcare resource utilization and costs during the 5-year follow-up period for DFU patients, with resource utilization and costs categorized by inpatient care, SOC visits, ED visits, and DFU-related procedures. The evaluated clinical factors and outcomes include baseline patient characteristics and comorbidities, wound status, LEA rates, and mortality rates. In addition, the evaluated hospitalization and outpatient details include procedures performed, LOS, 30-day readmissions, and clinic visits.

Analysis methodology at the public healthcare cluster level (2016–2017)

Second, we conducted an observational population health cohort study utilizing inpatient and outpatient EMR databases from June 2016 to December 2017 within our public healthcare cluster. The healthcare cluster is an integrated network of seven primary care polyclinics (2.4 million combined yearly attendances) and two acute care and tertiary hospitals (1,700 and 800 beds) [42]. The larger 1,700-bed hospital is the same institution which we performed the earlier hospital-level analysis. The healthcare cluster serves a multiethnic (Chinese, Malay, and Indian) and elderly (17% over 65 years) catchment population of 2.2 million in central and northern Singapore. The National Healthcare Group (NHG) Data Exchange Office retrieved clinical, administrative, and healthcare cost data from the Diabetes Chronic Disease Management Registry using the ICD9 and ICD10 diagnosis, surgical procedure, and service codes (Appendix 1). Clinical variables included demographic data, baseline comorbidities, cardiovascular profile, and DFU-related procedures. The analyzed outcomes included LEA rates (minor and major) and mortality rates. In addition, the analyzed administrative variables encompassed health service utilization at primary and tertiary care (ED attendance, inpatient admissions, LOS, and clinic visits). When compared to the earlier hospital-level analysis, both databases utilized are based on the same underlying EMR system. Repeat measurements were identified due to a unique national patient identification number and hence removed to avoid repeat analysis. Direct healthcare costs were calculated from a patient’s perspective (before government subsidies), including physician fees, inpatient hospital stays, procedures, supportive dressings, and adjuvant therapy. Indirect healthcare costs were not evaluated. Singapore’s healthcare system adopted a mixed financing system, whereby healthcare subsidies were derived from nationalized life insurance schemes and deductions from the compulsory savings plan *via* the Central Provident Fund [41].

Statistical analysis

All continuous data were expressed as mean ± standard deviation (SD) for normally distributed data and median + interquartile range (IQR) for data that were not normally distributed. Categorical data were expressed as percentages (%). No data imputations were conducted for the reported clinical biochemical markers. The number and costs of resource utilization were reported as the total for the study period and per patient-year. All DFU-related services were calculated as the number of discrete inpatient stays, ED visits, SOC visits, and procedures performed. Patient-year was calculated as the number of days a patient added to the denominator (i.e., days from the index date to cessation of therapy, death, or end of study period) divided by 365. The Kaplan–Meier method was used to estimate the unadjusted survival probabilities for all-cause mortality and major amputation. In addition, the stepwise Cox-proportional hazard (PH) model was performed to identify the risk factors for major amputation and all-cause mortality. Risk factors include age, sex, PAD, history of stroke, IHD, ESRF, and major LEA. A dummy coding of 0 and 1 was used to enter the nominal independent variables, except for age. The PH assumption was met and tested using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. In addition, variance inflation factor analysis was performed to check for multicollinearity; however, none was observed. The significance level was predetermined at $P < 0.05$ for all tests. All statistical analyses were performed using Microsoft Excel 2016 (Microsoft, Redmond, Washington) and R software version 3.6.1 (R Foundation, Vienna, Austria). This study was approved by the institution's ethics review board (National Healthcare Group Domain Specific Review Board 2019/00813 and 2021/01154).

Results

Analysis at the hospital level (2013–2017)

From January 2013 to December 2017, 1,729 patients received treatment for DFU (Table 1). The mean age was 63.4 years (standard deviation [SD] 12.59), with more than 50% aged 55–74 years (56.5%). The average follow-up time of patients during the 5-year observation period was 2.9 years. Most patients were males (64.4%), and a greater proportion of patients were of Indian ethnicity (18.4%), compared to the Singapore general population (9.0% in 2018) [43]. Almost three-quarters of patients had underlying PAD (74.8%), and one-sixth (14.5%) had peripheral neuropathy. The study population generally had good lipid control with a median cholesterol level of 4.8 mmol/L (interquartile range [IQR] 2.1) but poor glycemic control with median hemoglobin A1c (HbA1c) at 9.9% (IQR 14.8). Each patient had a mean of 6.1 documented wounds and 2.1 DFU per year (total wound documentation n = 10,490). Most documented wounds were located on the toes (39.2%) or foot plantar surface (34.4%).

Subgroup analysis of patient characteristics for individuals with ulcers-only, minor LEA, or major LEA revealed that those who underwent major LEA were more likely to be older (mean age 65.2 years, $P = 0.004$) and male (70.1%, $P < 0.001$), with comorbidities of hypertension (95.2%, $P = 0.003$), IHD (68.9%, $P < 0.001$), CKD (50.6%, $P = 0.029$), ESRF (40.5%, $P < 0.001$), PAD (99.2%, $P < 0.001$), and raised C-reactive protein (CRP) levels (median 70.7 mg/L, $P < 0.001$).

Within the study population, the mean healthcare cost for hospital (inpatient and outpatient) DFU care was US$6,615,437 (SG$9,381,748) per year, with the respective mean cost per patient-year for ulcers-only, minor amputations, and major amputations at US$3,368 (SG$4,776), US$10,468 (SG$14,845), and US$30,131 (SG$42,730) (Table 2). The mean ED visit was 1.0 per patient-year, the mean SOC visit was 8.1 per patient-year, and the mean hospital admission was 0.58 per patient-year, with 30-day readmission rates at 12.7%. The mean inpatient LOS for ulcers-only, minor amputations, and major amputations was 13.3, 20.5, and 59.6 days, respectively. More than one in three patients underwent toe amputation (36.4%), and more than one in six underwent trans-metatarsal amputation (TMA) (16.9%). However, more than one in fifteen patients underwent major LEA (6.5%).

In terms of time to event (survival outcomes), the major LEA-free survival rates were 97.4% and 91.0% at 1 and 5 years, respectively. However, the minor LEA-free survival rates were 80.9% and 56.9% at 1 and 5 years, respectively (Table 3, $P < 0.001$). The overall survival rates were 93.8% and 62.1% at 1 and 5 years, respectively. Subgroup survival analysis showed higher mortality signals among patients who underwent major LEA (5-year survival at 32.9%) (Figure 1, $P < 0.001$). This subgroup was characterized by advanced age (Figure 2, $P < 0.001$), PAD (5-year survival at 58.9%), IHD (5-year survival at 50.1%), previous stroke (5-year survival at 52.3%), and ESRF (5-year survival at 50.8%) (Figure 3, $P < 0.001$).

Independent predictors for all-cause mortality were age (hazard ratio [HR] of 1.1, $P < 0.001$), major amputation (HR of 1.8, $P < 0.001$), PAD (HR of 1.4, $P = 0.015$), IHD (HR of 10.8, $P < 0.001$), previous stroke (HR of 1.2, $P = 0.041$), and ESRF (HR of 1.4, $P = 0.002$) (Table 4). Concerning major LEA, the overall rate was 6.5%, and the independent predictors were age (HR of 1.0, $P = 0.002$), PAD (HR of 27.9, $P < 0.001$), IHD (HR of 12.3, $P = 0.033$), and ESRF (HR of 1.9, $P = 0.002$) (Table 4). Regarding minor LEA, the overall rate was 36.4%, and the independent predictors were male (HR of 1.3, $P < 0.001$) and PAD (HR of 7.4, $P < 0.001$) (Table 4).

Analysis at the healthcare cluster level (2016–2017)

A total of 5,462 patients with DFU were managed within the public healthcare cluster from June 2016 to December 2017, with results similar to those from the hospital level from 2013 to 2017. Within the study population, the mean age was 71.6 years, and 53.8% were male (Table 5). The ethnic compositions of Chinese, Malay, and Indian were 65.6%, 14.1%, and 13.4%, respectively. The majority (59.3%) were nonsmokers, and 22.7% were ex-smokers or current smokers. Patients had significant cardiovascular comorbidities: 95.0% with hypertension, 93.0% with dyslipidemia, 39.7% with IHD, 37.7% with previous stroke, and 20.5% with ESRF. The mean Charlson Comorbidity Index (CCI) [44] was 3.9, with a mean HbA1c at 7.7% among the study population. At 1 year, the mortality rate was almost 1 in 3 at 30.7%, with minor LEA-free survival at 65.2% and major LEA-free survival at 65.9% (Table 6). Interestingly, for patients diagnosed with DFU, the mean time from DFU to the first minor LEA was 56.7 days, the mean time to the first major LEA was 82.6 days, and the mean time to mortality was 118.6 days. Regarding healthcare service utilization, the mean number of hospital admissions was 2.5 per year, and the mean cumulative LOS amounted to 26.3 days. In addition, the mean of primary care polyclinic episodes was 1.8, with a mean hospital SOC episode of 2.8. The mean direct healthcare cost per patient was US$11,845 (SG$15,938).

Table 1: Characteristics of patients who presented with DFU at a university tertiary hospital (2013–2017).

Characteristics	All (*n* = 1,729)		Ulcer-only (*n* = 1,108)		Minor LEA (*n* = 513)		Major LEA (*n* = 108)		*P* value
	n	%	*n*	%	*n*	%	*n*	%	
Age, mean (SD)	63.4 (12.59)		63.9 (12.97)		62.0 (12.09)		65.2 (10.09)		**0.004[a]**
18–34	22	1.3	14	1.3	8	1.6	0	0	
35–44	97	5.6	64	5.8	31	6.0	2	1.9	
45–54	318	18.4	192	17.3	108	21.1	18	16.7	
55–64	529	30.6	335	30.2	164	32.0	30	27.8	
65–74	448	25.9	275	24.8	134	26.1	39	36.1	
75+	315	18.2	228	20.6	68	13.3	19	17.6	
Sex									**<0.001[b]**
Male	1,113	64.4	675	60.6	366	63.6	72	70.1	
Female	616	35.6	433	39.4	147	36.4	36	29.9	
Ethnicity									0.626[b]
Chinese	1,061	61.4	670	60.9	317	61.6	74	69.0	
Indian	318	18.4	211	18.9	91	18.2	16	16.6	
Malay	234	13.5	147	13.2	75	14.5	12	11.0	
Others	116	6.7	80	7.0	30	5.7	6	3.5	
Comorbidities									
Diabetic retinopathy	764	44.0	469	42.5	248	48.3	47	39.0	0.076[b]
Hypertension	1,534	88.7	963	86.7	468	91.9	103	95.2	**0.003[b]**
Dyslipidemia	1,618	93.6	1034	93.5	481	94.0	103	95.1	0.695[b]
Ischemic heart disease	855	49.9	519	47.1	262	51.6	74	68.9	**<0.001[b]**
History of stroke	425	25.6	271	26.3	121	23.0	33	30.1	0.307[b]
Chronic kidney disease	1,031	61.6	661	61.3	318	64.4	52	50.6	**0.029[b]**
End-stage renal failure	408	23.2	233	20.9	127	24.3	48	40.5	**<0.001[b]**
Peripheral arterial disease	1,292	74.8	703	62.8	482	95.1	107	99.2	**<0.001[b]**
Peripheral neuropathy	261	14.5	177	15.5	66	12.2	18	15.9	0.238[b]
Biochemical markers									
Cholesterol (median, IQR), *n* = 1341	4.8 (2.1)		4.9 (2.0)		4.6 (2.0)		4.8 (2.2)		0.062[a]
HbA1c (median, IQR), *n* = 1542	9.9 (14.8)		9.8 (4.3)		10.1 (4.2)		10.0 (3.7)		0.127[a]
CRP (median, IQR), *n* = 1596	43.4 (378.1)		31.5 (98.4)		58.6(136.0)		70.7(134.0)		**<0.001[a]**

Documented wound anatomy (*n* = 10,490)									
Toes	4,109	39.2	-	-	-	-	-	-	-
Foot plantar	3,613	34.4	-	-	-	-	-	-	-
Foot dorsum	1,187	11.3	-	-	-	-	-	-	-
Heel	1,008	9.6	-	-	-	-	-	-	-
Ankle	573	5.5	-	-	-	-	-	-	-

[a]Kruskal–Wallis test, [b]chi-squared test.

Abbreviations: CRP: C-reactive protein; DFU: diabetic foot ulcer; IQR: interquartile range; LEA: lower extremity amputation; SD: standard deviation;

Table 2: Costs and healthcare utilization for patients who presented with DFU at a university tertiary hospital (2013–2017).

Components	Cost
Total healthcare costs, 2013-2017 US$	33,077,183
Cumulative 2013–2017 (SG$)	(46,908,742)
Mean cost per year	6,615,437 (9,381,748)
Costs, per patient-year, US$ (SG$)	
Mean	7,152 (10,142)
Per ulcer	3,368 (4,776)
Per minor LEA	10,468 (14,845)
Per major LEA	30,131 (42,730)

Components	Episodes	Mean utilization
Services		
Specialist outpatient clinic	37,447	8.1
Emergency department	4,605	1.0
Hospital admission	2,679	0.58
30-day readmission rate	12.7%	-
Mean inpatient length of stay (days)	16.6	-
Per ulcer-only	13.3	-
Per minor LEA	20.5	-
Per major LEA	59.6	-
Components	Episodes	
Interventions		
Debridement	1,803	
Revascularization	667	
Minor LEA		
Toe amputations	630 (36.4%)	-
Transmetatarsal	293 (16.9%)	-
Major LEA	113 (6.5%)	-

Abbreviations: DFU: diabetic foot ulcer; LEA: lower extremity amputation; SG: Singapore; US: United States.

Table 3: Event-free survival rate (major LEA, major LEA, and overall) for patients who presented with DFU at a university tertiary hospital (2013–2017)

Variables	Probability of surviving, % (event: major LEA)			Probability of surviving, % (event: minor LEA)			Probability of surviving, % (event: overall death)		
	1 year	3 years	5 years	1 year	3 years	5 years	1 year	3 years	5 years
Overall	97.4	94.7	91.0	80.9	67.9	56.9	93.8	79.5	62.1
Gender									
Male	97.5	94.9	90.8	79.3	65.0	52.7	94.2	80.0	62.6
Female	97.1	94.2	91.5	83.7	73.0	64.2	92.9	78.6	61.2
Age groups									
18 < 35	100	100	100	77.3	72.7	62.3	100	100	94.7
35 < 45	99.0	99.0	95.7	84.5	66.2	61.9	97.9	92.2	87.0
45 < 55	97.4	96.2	91.6	78.9	66.4	53.6	96.1	88.3	72.4
55 < 65	97.5	95.1	92.3	81.2	69.5	58.2	95.8	85.2	70.0
65 < 75	97.2	92.7	87.7	81.2	65.8	53.1	94.7	78.1	58.0
≥75	96.6	93.3	91.7	81.1	69.4	62.9	84.8	56.5	33.8
LEA									
Major	-	-	-	-	-	-	88.8	61.7	32.9
Minor	-	-	-	-	-	-	94.7	83.0	62.8
None	-	-	-	-	-	-	93.8	79.5	64.7
IHD									
Yes	96.1	92.8	87.6	81.0	65.4	51.8	92.3	72.9	50.1
No	98.6	96.6	94.5	80.8	70.3	62.0	95.2	86.4	76.6
PAD									
Yes	96.5	92.9	88.5	75.6	59.2	47.0	93.2	76.9	58.9
No	99.5	99.5	99.5	96.8	94.3	89.5	95.5	87.7	74.1
Stroke									
Yes	96.6	92.8	90.2	81.5	67.5	55.0	91.9	71.8	52.3
No	97.6	95.3	91.3	80.7	68.0	57.4	94.4	82.1	65.8
ESRF									
Yes	94.4	91.0	83.5	83.0	67.1	49.3	92.0	74.6	50.8
No	98.3	95.9	93.6	80.3	68.2	59.7	94.3	81.1	66.6

Abbreviations: DFU: diabetic foot ulcer; ESRF: end-stage renal failure; IHD: ischemic heart disease; LEA: lower extremity amputation; PAD: peripheral arterial disease.

Table 4: Multivariate Cox-proportional hazard model for all-cause mortality, major LEA, and minor LEA in patients who presented with DFU at a university tertiary hospital (2013–2017)

Covariates	Hazard Ratio	95% CI Lower	95% CI Upper	z	*P* value
All-cause mortality[a]					
Age (years)	1.07	1.05	1.08	9.53	**<0.001**
Major LEA	1.80	1.35	2.40	4.03	**<0.001**
PAD	1.37	1.06	1.77	2.43	**0.015**
IHD	10.77	3.28	35.34	3.92	**<0.001**
Previous stroke	1.22	1.01	1.48	2.05	**0.041**
ESRF	1.37	1.12	1.68	3.04	**0.002**
Age*IHD	0.97	0.96	0.99	−2.99	**0.003**
Major LEA[b]					
Age (years)	1.04	1.01	1.07	3.04	**0.002**
IHD	12.27	1.21	124.19	2.12	**0.033**
PAD	27.95	3.98	200.64	3.31	**<0.001**
ESRF	1.92	1.27	2.90	3.11	**0.002**
Age*IHD	0.97	0.94	1.00	−1.85	0.064
Minor LEA[c]					
PAD	7.39	1.13	1.60	10.84	**<0.001**
Male	1.35	5.15	10.61	3.34	**<0.001**

[a]Likelihood ratio test = 279.3, $P < 0.001$; Wald test = 228.6, $P < 0.001$.

[b]Likelihood ratio test = 80.6, $P < 0.001$; Wald test = 36.7, $P < 0.001$

[c]Likelihood ratio test = 232.9, $P < 0.001$; Wald test = 130.1, $P < 0.001$.

Abbreviations: CI: confidence interval; DFU: diabetic foot ulcer; ESRF: end-stage renal failure; IHD: ischemic heart disease; LEA: lower extremity amputation; PAD: peripheral arterial disease.

Table 5: Characteristics of patients who presented with DFUs at a public healthcare cluster (2016–2017)

Variables		***n* = 5,462**
Age, mean (SD)		71.6 (13.2)
Gender		
	Male	2,936 (53.8)
	Female	2,526 (46.3)
Ethnicity		
	Chinese	3,583 (65.6)
	Malay	768 (14.1)
	Indian	733 (13.4)
	Others	378 (6.9)
Smoking status		
	Nonsmoker	3,239 (59.3)
	Ex-smoker	655 (12.0)
	Current smoker	582 (10.7)
	Unknown	986 (18.1)
History of LEA		
	Previous minor LEA within **the** past 3 years	164 (3.0)
	Previous minor LEA within the past 1 year	54 (1.0)
	Previous major LEA within the past 3 years	129 (2.4)
	Previous major LEA within the past 1 year	42 (0.8)
Medications		
	Antiplatelet	3,230 (59.1)
	Anticoagulant	969 (17.7)
	Lipid-lowering	4,311 (78.9)
	Antihypertensive	4,546 (83.2)
	Insulin	1,657 (30.3)
	Oral DM medications	3,697 (67.7)
Type of DM medications		
	Not on DM medications	1,364 (25.0)
	Oral DM medications only	2,441 (44.7)

	Insulin only	401 (7.3)
	Oral DM medications and insulin	1,256 (23)
HbA1c, mean (SD)		7.7 (2.1)
Comorbidities		
	CCI, mean (SD)	3.9 (2.1)
	Hypertension	5,188 (95.0)
	Dyslipidemia	5,077 (93.0)
	Diabetic retinopathy	1,787 (32.7)
	Dementia	1,320 (24.2)
	Ischemic heart disease	2,166 (39.7)
	History of stroke	2,058 (37.7)
	End-stage renal failure	1,117 (20.5)
CKD severity		
	No CKD	993 (18.2)
	Mild	1,477 (27.0)
	Moderate	1,695 (31.0)
	Severe	1,297 (23.8)

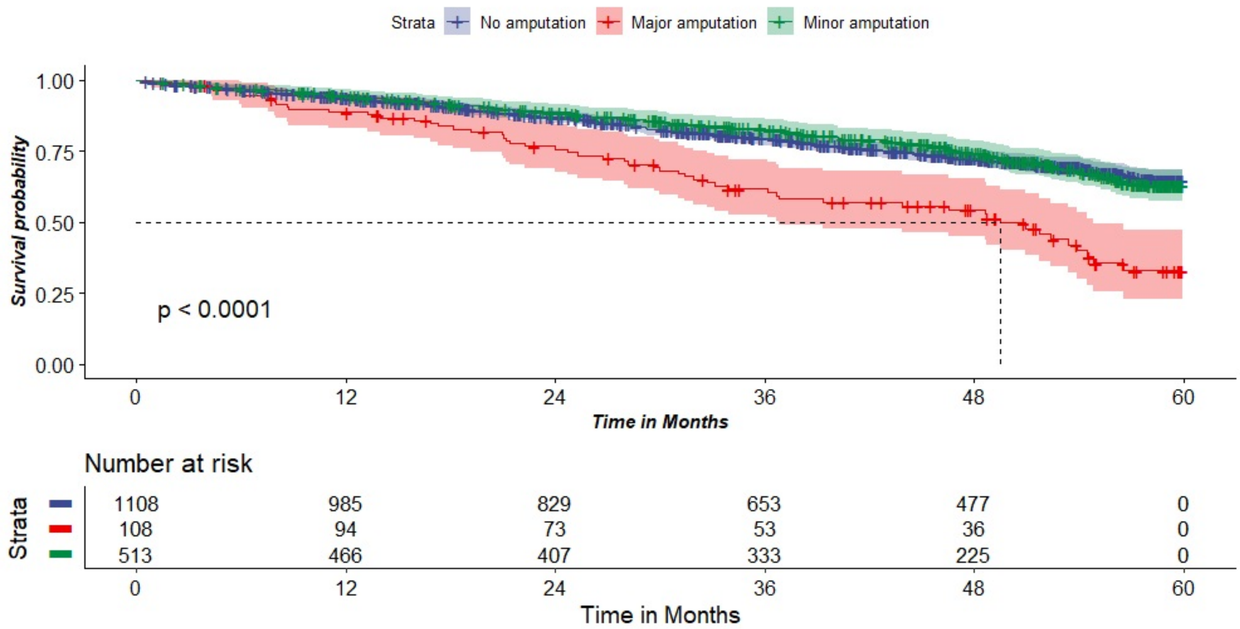
Abbreviations: CCI: Charlson Comorbidity Index; CKD: chronic kidney disease; DFU: diabetic foot ulcer; DM: diabetes mellitus; LEA: lower extremity amputation; LEAPP: lower extremity amputation prevention program; SD: standard deviation.

Table 6: 1-year outcomes of patients who presented with DFU at a public healthcare cluster (2016–2017).

Outcomes	***n* = 5,462**
Minor LEA	259 (4.7)
Major LEA	259 (4.7)
Mortality	1,677 (30.7)
Minor LEA-free survival	3,561 (65.2)
Major LEA-free survival	3,599 (65.9)
Mean days from DFU to first minor LEA (SD)	56.7 (21.2)
Mean days from DFU to first major LEA (SD)	82.6 (7.5)
Mean days from DFU to mortality (SD)	118.6 (35.5)
Mean hospital admissions (SD)	2.5 (1.6)
Mean emergency department episodes (SD)	2.7 (1.9)
Mean cumulative length of stay, days (SD)	26.3 (22.0)
Mean day surgery episodes (SD)	0.2 (1.2)
Mean primary care polyclinic episodes (SD)	1.8 (1.2)
Mean hospital specialist outpatient clinic episodes (SD)	2.8 (1.8)
Mean direct healthcare cost per patient, US$ (SG$)	11,845 (15,938)

Abbreviations: DFU: diabetic foot ulcers; LEA: lower extremity amputation; SD: standard deviation; SG: Singapore; US: United States.

Figure 1: Survival analysis comparing patients with ulcers-only, minor amputation, and major amputation at the hospital level (2013–2017).



<u>Figure 2: Survival analysis by age groups at the hospital level (2013–2017).</u>

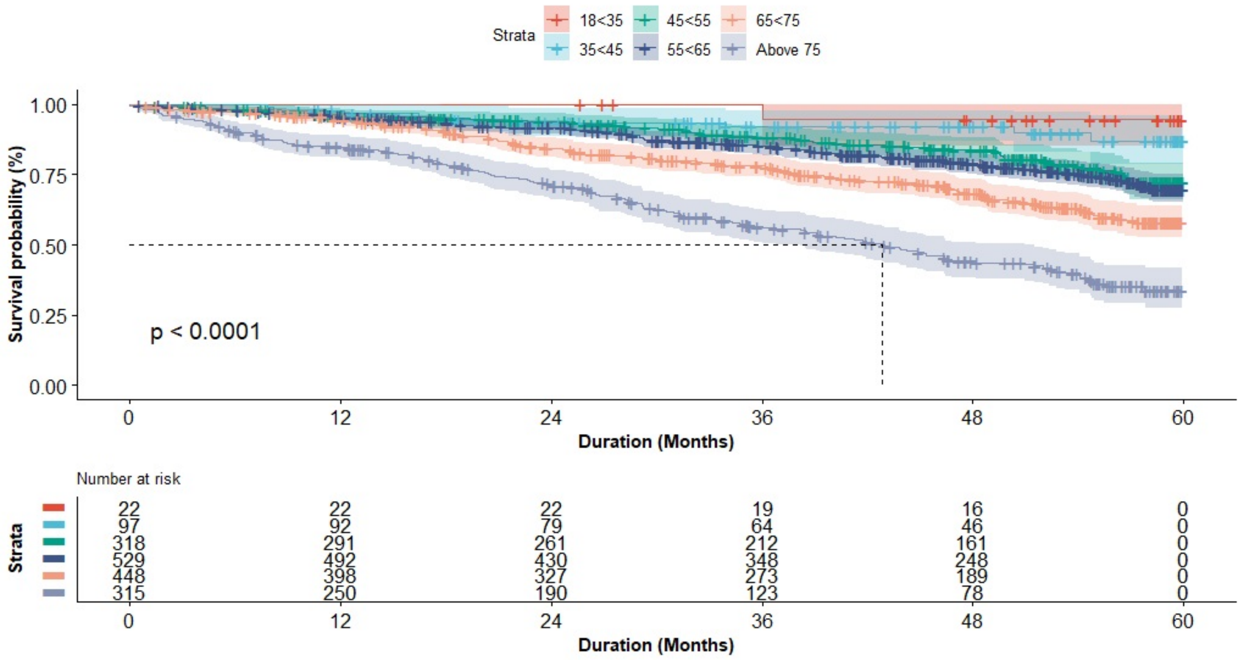
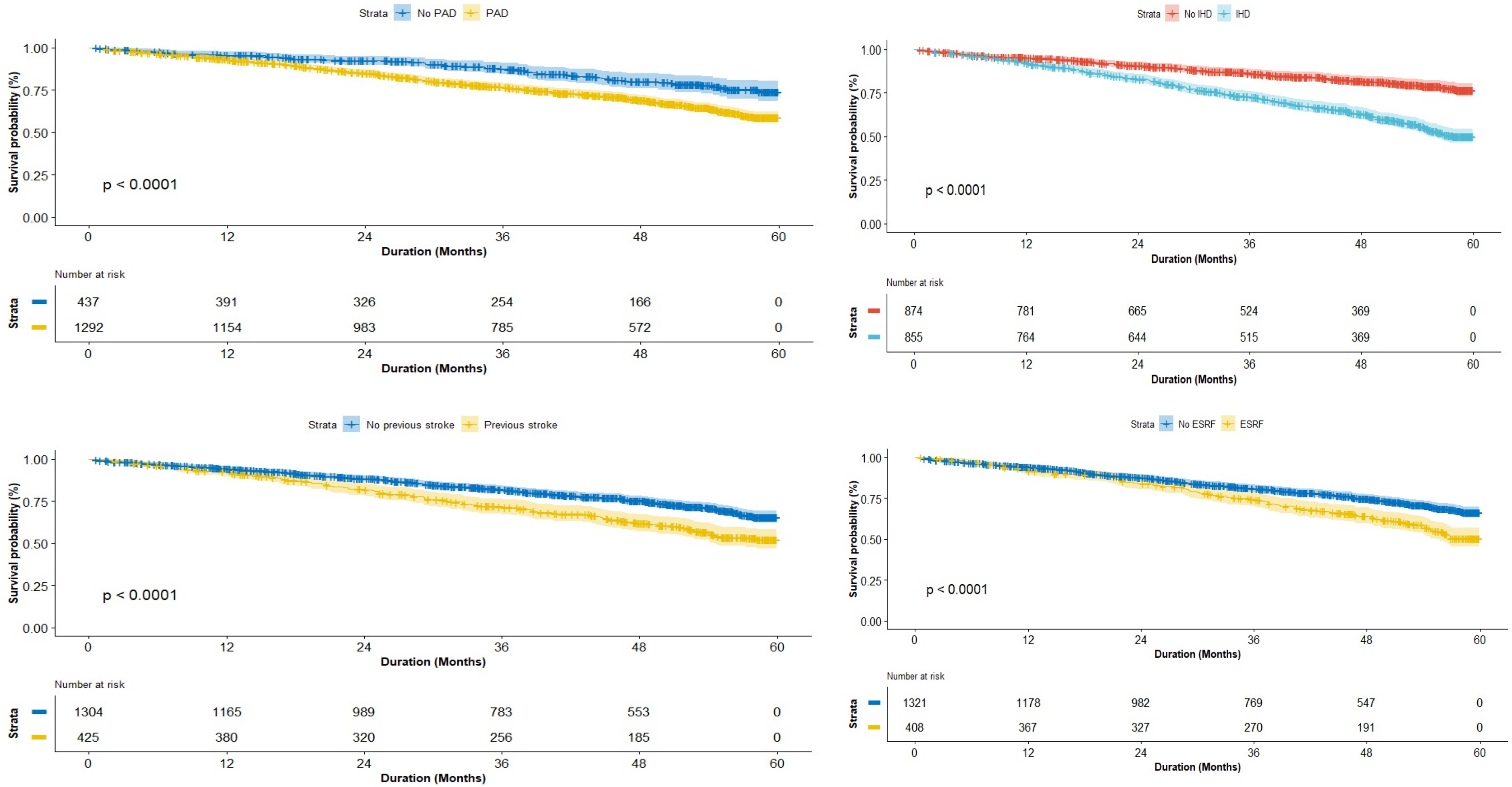


Figure 3: Survival analysis in patients with and without PAD (a), IHD (b), previous stroke (c), and ESRF (d) at the hospital level (2013–2017).



Abbreviations: ESRF: end stage renal failure ; IHD: ischaemic heart disease ; PAD: peripheral arterial disease

Chapter 3: Evaluation of the Clinical and Economic Outcomes of an MDT Approach in a LEAPP Clinic for DFU Care

Summary

This chapter presents an evaluation of the clinical and economic outcomes of an MDT approach in a lower extremity amputation prevention program (LEAPP) for DFU care. A case–control study involving 84 patients with DFUs was performed from January 2017 to October 2017 (retrospective control) *versus* 117 patients with DFUs from December 2017 to July 2018 (prospective LEAPP cohort). A comparison of the clinical outcomes between the retrospective and LEAPP cohorts demonstrated a significant decrease in the mean time from referral to index clinic visit (38.6 *vs*. 9.5 days, $P < 0.001$), an increase in outpatient podiatry follow-up (33% *vs*. 76%, $P < 0.001$), a decrease in 1-year minor LEA rate (14% *vs*. 3%, $P = 0.007$), and a decrease in the 1-year major LEA rate (9% *vs*. 3%, $P = 0.05$). The cost avoidance simulation demonstrated an annualized cost avoidance of US$1.9 million (SG$2.5 million) for patients within the LEAPP cohort. Similar to the data from Western societies, an MDT approach within an Asian population *via* an expedited access LEAPP clinic for patients with DFUs revealed a significant improvement in clinical and economic outcomes.

Methodology

A case–control (prospective cohort comparison against a retrospective cohort) study was conducted at a university tertiary hospital in Singapore (as described in Chapter 2). All patients >21 years with preexisting DM were included and referred for foot ulcers (at or distal to malleolus). Patients with venous ulcers or ulcers of mixed arteriovenous etiology were excluded from the study. This study followed the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [45].

A retrospective analysis was performed for patients referred to the conventional vascular surgery SOC from January 1, 2017, to October 31, 2017. However, a prospective analysis was performed for patients referred to the multidisciplinary LEAPP clinic from December 1, 2017, to June 30, 2018. All patients had completed a minimum of 1-year follow-up at the time of analysis. Figure 4 shows the clinical and referral workflow differences between the retrospective cohort and the LEAPP clinic. A total of 11 conventional vascular surgery SOC room sessions were conducted weekly within the retrospective cohort.

Within the prospective LEAPP cohort, the same 11 conventional vascular surgery SOC room sessions ran concurrently with the new LEAPP clinics. There were two LEAPP clinic room sessions per week, which represented a 9.1% increase in clinic resource allocation between the retrospective and prospective cohorts. Although the retrospective cohort patients were primarily examined by vascular surgeons at conventional vascular surgery SOCs, with patients requiring separate appointments to be reviewed by endocrinology, podiatry, or both, the LEAPP clinic adopted an MDT approach in managing patients with DFUs, involving podiatry, vascular surgery, and endocrinology as core components. Support members included diabetic nurse clinicians, wound nurses, orthopedic surgeons, infectious disease physicians, prosthetics and orthotic technicians, and plastic and reconstructive surgeons. Referral sources to the clinic included patients with DFUs from primary care, ED, and tertiary SOCs, as well as wards after discharge. Referrals were screened by a vascular surgeon three times a week. Patients who fulfilled the inclusion criteria were scheduled for an appointment at a LEAPP clinic on the earliest available date, usually within the following five working days. The LEAPP clinic was held every Tuesday and Thursday morning, and an average of 12–15 patients were reviewed at each session. In each clinic session, a vascular surgeon and endocrinologist reviewed the patients in conjunction with two podiatrists, a diabetic nurse clinician, and/or a wound nurse. In addition to providing expedited access, the key interventions at the LEAPP clinic included optimization of glycemic control and medical risk factors, prompt revascularization, active wound care, appropriate offloading, and patient education. According to the IWGDF guidelines [30], patients with neuropathic ulcers received medical optimization, wound care, and appropriate offloading. Nevertheless, patients with ischemic ulcers received medical optimization, revascularization, wound care, and appropriate offloading.

Factors and outcomes were evaluated using descriptive statistics. Percentages were used for categorical data, and means with SDs were used for continuous data. Between-group comparisons for categorical data were performed using chi-squared tests, whereas those for continuous data were performed using Student's *t*-test. P values < 0.05 were considered statistically significant, and all P values were two-tailed. All statistical analyses were performed using Microsoft Excel 2016 (Microsoft, Redmond, Washington) and R software version 3.6.1 (R Foundation, Vienna, Austria).

Health economic analysis involved evaluating cost avoidance for retrospective and prospective cohorts. In a 6-month period from the index clinic appointment date, the gross healthcare costs of any inpatient admission, LEA, DFU-related SOC visits, and DFU-related primary care visits at primary care polyclinics were calculated (Figure 5). The major LEA rate of LEAPP patients was adjusted to match the patient profiling of the retrospective cohort by weighted logistic regression. The covariates considered in risk adjustment included age, gender, ethnicity, chronic disease prevalence (e.g., CKD stage 3, coronary heart disease, heart failure, and previous stroke), and previous major LEA. Based on the risk-adjusted major LEA rates between the two groups, a cost avoidance simulation was performed using the summation of gross charges of any episode 1 month before an index LEA episode and any episode 2 months after an index LEA episode (Figure 6). This study was approved by the institution's ethics review board (National Healthcare Group Domain Specific Review Board 2020/00500).

Results

From January 2017 to October 2017, 84 patients fulfilled the inclusion criteria within the retrospective cohort, and from December 2017 to July 2018, 117 patients fulfilled the inclusion criteria within the LEAPP cohort. Both groups demonstrated similar baseline characteristics, with a mean glycated hemoglobin (HbA1c) of 8%, and most patients had comorbidities of hypertension, hyperlipidemia, and CKD stage 3 (Table 7).

A comparison of the clinical outcomes between the retrospective and LEAPP cohorts revealed a significant decrease in the mean time from referral to index clinic visit (38.6 *vs*. 9.5 days, $P < 0.001$) and the mean time from index visit to vascular diagnostic imaging and revascularization (24.2 *vs*. 9.9 days, $P < 0.001$, and 39.0 *vs*. 32.6 days, $P = 0.015$, respectively) (Table 8). After index clinic visits, a considerable increase was observed in outpatient podiatry follow-up (33% *vs*. 76%, $P < 0.001$) within the LEAPP cohort. However, 10%–14% of patients within the LEAPP cohort underwent further medical optimization, such as single antiplatelet therapy, statin therapy, and diabetes medication optimization. Significantly, there was a marked decrease in 1-year the minor amputation rates within the LEAPP cohort (14% *vs*. 3%, $P = 0.007$) and a decrease in the major amputation rates within the LEAPP cohort (9% *vs*. 3%, $P = 0.050$).

When evaluating the number of healthcare-related episodes and costs within 6 months from the index clinic visit and related healthcare costs (Figure 5), no statistical significance was detected between the retrospective and LEAPP cohorts (Table 9). However, the LEAPP group showed a trend toward more specialist and primary care outpatient clinic visits (+5.1 and +3.0 differences per patient, respectively) with increased healthcare costs (+US$137; SG$184 and +US$118; +SG$158 differences per patient, respectively). This is balanced against reduced inpatient gross charge per patient within the LEAPP cohort (−US$1,044; −SG$1,404 differences), resulting in a decreased total gross charge per patient within 6 months (US$9860; SG$13 253 for retrospective cohort *vis-à-vis* US$9,408; SG$12,645 for LEAPP cohort), representing a 4.6% reduction.

The risk-adjusted major LEA rates for the retrospective and LEAPP cohorts were 13.1% and 8.8%, respectively, using weighted logistic regression for covariates of age, gender, ethnicity, chronic disease prevalence, and previous major LEA. Accordingly, LEAPP will likely reduce the major LEA rate by 33% compared with the retrospective control group. Hence, by using a 33% reduction in major LEA, cost avoidance simulation by summation of gross charges of any episode 1 month before an index LEA episode and any episode 2 months after an index LEA episode (Figure 6) resulted in an annualized cost avoidance of US$1.9 million (SG$2.5 million) for patients within the LEAPP cohort (Table 10).

Table 7: Baseline characteristics between retrospective and LEAPP cohorts.

	Retrospective cohort (*n* = 84)	**LEAPP cohort (*n* = 117)**	***P* value**
Mean age in years (SD)	63.4 (12.6)	63.9 (12.8)	N/S
Male gender (%)	47 (56)	77 (66)	N/S
Ethnicity (%)			N/S
Chinese	62 (74)	74 (63)	
Malay	6 (7)	11 (9)	
Indian	11 (13)	25 (21)	
Others	5 (6)	7 (6)	
Mean HbA1c % (SD)	8.0 (4.3)	8.0 (4.2)	N/S
Chronic diseases (%)			
Hypertension	75 (89)	106 (91)	N/S
Dyslipidemia	77 (92)	112 (96)	N/S
Chronic kidney disease stage 3	54 (64)	71 (61)	N/S
Coronary heart disease	39 (46)	50 (43)	N/S
Heart failure	24 (29)	23 (20)	N/S
Previous stroke	29 (35)	32 (27)	N/S

Abbreviations: LEAPP: lower extremity amputation prevention program; N/S: non-significant; SD: standard deviation.

Table 8: Clinical outcomes between retrospective and LEAPP cohorts.

	Retrospective cohort (*n* = 84)	**LEAPP cohort (*n* = 117)**	***P* value**
Mean time from referral to index visit (days)	38.6	9.5	<0.001
Mean time from index visit to vascular diagnostic imaging (days)	24.2	9.9	<0.001
Mean time from index visit to revascularization	39.0	32.6	0.015
Further medical optimization (%)			
Single antiplatelet therapy	N/A	16 (14)	N/A
Statin therapy	N/A	12 (10)	N/A
Diabetes optimization	N/A	15 (13)	N/A
Further podiatrist follow-up (%)	28 (33)	89 (76)	<0.001
Amputation rates (%)			
1-year minor amputations	12 (14)	4 (3)	0.007
1-year major amputations	8 (9)	3 (3)	0.050

Abbreviations: LEAPP: lower extremity amputation prevention program; N/A: not available.

Table 9: Healthcare-related episodes and costs within 6 months from the index clinic visit.

	Retrospective cohort (*n* = 84)	**LEAPP cohort (*n* = 117)**	**Change***
Hospital specialist outpatient clinics	8.9	14.0	+5.1
Gross charge per patient, US$ (SG$)	1,246 (1,675)	1,383 (1,859)	+137 (+184)
Primary care outpatient clinics	7.9	10.9	+3.0
Gross charge per patient, US$ (SG$)	407 (547)	525 (705)	+118 (+158)
Inpatient admissions	0.9	0.9	0
Gross charge per patient, US$ (SG$)	7,910 (10,632)	6,866 (9,228)	−1,044 (−1,404)
Emergency department episodes	0.9	0.9	0
Gross charge per patient, US$ (SG$)	246 (330)	232 (312)	−14 (−18)
Ambulatory surgery procedures	0.1	0.3	+0.2
Gross charge per patient, US$ (SG$)	51 (69)	402 (540)	+351 (+471)
Total gross charge per patient within 6 months, US$ (SG$)	**9,860 (13,253)**	**9,408 (12,645)**	**−452 (−608)**
Percentage reduction			**4.6%**

*All results are statistically nonsignificant.

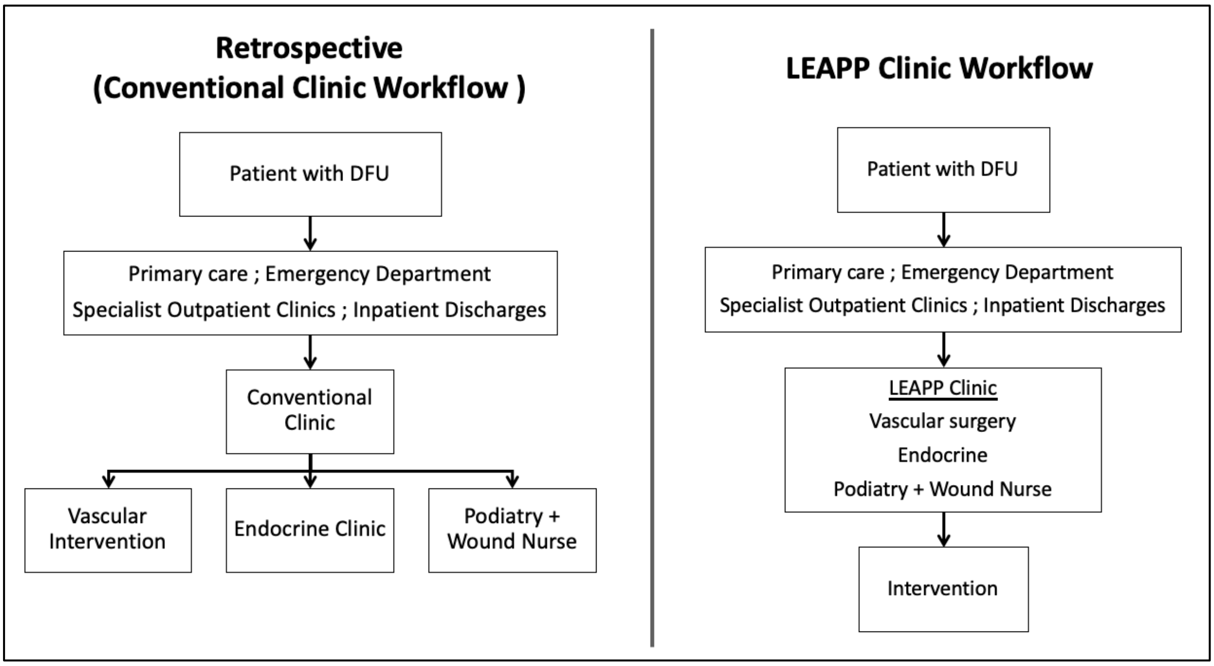
Abbreviations: N/S: nonsignificant; SG: Singapore; US: United States.

<u>Table 10: Simulated annualized cost avoidance for major LEA.</u>

	2018 attributable gross charge, US$ million (SG$ million)	**Simulated cost avoidance for 33% major LEA reduction US$ million (SG$ million)**
Major LEA episodes	4.5 (6.0)	1.5 (2.0)
Other episodes	1.0 (1.4)	0.4 (0.5)
Total	5.5 (7.4)	**1.9 (2.5)**

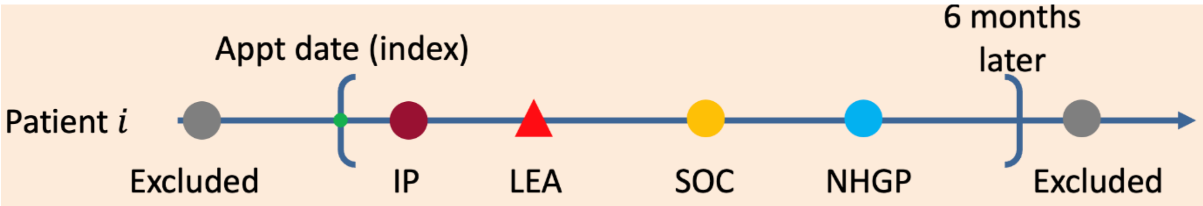
Abbreviations: LEA: lower extremity amputation; SG: Singapore; US: United States.

Figure 4: Workflow differences between the retrospective and LEAPP clinics.



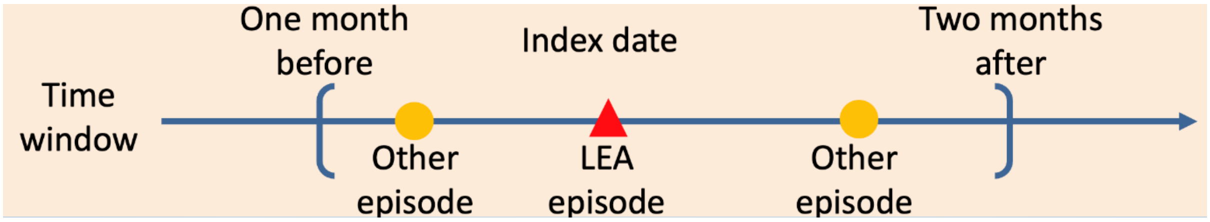
Abbreviations: DFU: diabetic foot ulcer; LEAPP: lower extremity amputation prevention programme

Figure 5: Gross healthcare costs from the index clinic appointment, with a 6-month time frame of any inpatient admission (IP), lower extremity amputations (LEAs), DFU-related specialist outpatient clinic visits (SOC), and DFU-related primary care visits at polyclinics (NHGP).



Abbreviations: DFU: diabetic foot ulcer; IP: inpatient admissions; LEA: lower extremity amputation; LEAPP: lower extremity amputation prevention programme; NHGP: National Healthcare Group Polyclinics SOC: specialist outpatient clinic

Figure 6: Cost avoidance Simulation is performed by summation of gross charges of any episode 1 month before an index LEA episode and any episode 2 months after an index LEA episode.



Abbreviations: LEA: lower extremity amputation

Chapter 4: Mixed-Methods Evaluation on Care Gaps for DFU Care at the Healthcare Cluster Level With Resultant Health Systems Innovation Methodology to DEFINITE Care

Summary

As demonstrated in earlier parts of this study, there is a heavy clinical and economic burden associated with diabetic foot disease in Singapore. Pilot results from the MDT LEAPP clinic showed reduced LEA rates with potential healthcare cost savings. Consequently, a multi-disciplinary and inter-institutional Diabetic Foot Workgroup (DFW) was convened within our public healthcare cluster. We used mixed methods (qualitative discussions and quantitative polls) to identify existing health service deficiencies for DFU care. In addition, by referencing international guidelines and best-practice DFU-related health service literature, we tailored an institution-specific DFU program for scaling up across the healthcare cluster.

Methodology

Mixed-methods evaluation on care gaps for DFU care at the healthcare cluster level

In 2019, a multi-disciplinary and inter-institutional DFW was convened within our public healthcare cluster, with key multi-disciplinary leadership from involved institutions: myself (tertiary care vascular surgery), Dr. ET (primary care physician), Dr. SC (tertiary vascular surgery), Dr. LHL (tertiary care endocrinology), Dr. DO (tertiary care vascular surgery), and Dr. HWH (tertiary care endocrinology), supported by multiple sub-specialty members from podiatry, nursing, orthopedics, and administrators (*n* = 19) (Table 11). DFW was under the auspice of the healthcare cluster's DM Steering Committee, which oversaw other corresponding workgroups to improve DM education, DM reporting dashboard, and tiered weight management efforts.

DFW members fortnightly conducted meetings between January 2020 and July 2020 (*n* = 12) involving qualitative discussions to identify health service deficiencies for DFU care. At the primary care level, there is currently a DM Foot Screening and Surveillance, Treatment, Escalation Program (DM Foot STEP), which provides Diabetic Foot Screening (DFS) following Singapore's National DM Foot Assessment guidelines [46]. In addition, Foot Surveillance (FS) exists under the umbrella of DM Foot STEP, which targets patients with moderate- and high-risk DM foot, providing guideline-based foot assessment and additional foot education to empower patients in the foot care journey (Figure 7). As discussed in Chapter 3, an MDT-style LEAPP clinic was piloted at a single hospital. This initiative resulted in a significant improvement in the clinical and economic outcomes for patients with DFU.

Despite the presence of DM Foot STEP and LEAPP programs, DFW members identified four major deficiencies within our healthcare cluster during the delivery of DFU care:

1. Outpatient care:
    a. Primary care polyclinics: although DFS is available at all seven polyclinics, the FS program is only available at two of seven sites. Due to the lack of a podiatry workforce, DFS and FS require upskilled nurses trained by podiatrists.
    b. Hospitals: there was difficulty scaling up the services at the hospital that piloted the LEAPP clinic owing to constraints with the podiatry workforce. At the other hospital, coordinated MDT care for patients with DFUs in an outpatient setting is necessary. This results in a lack of uniformity in providing rapid access to MDT LEAPP clinic services for patients referred from primary care to tertiary care.
2. Co-management of care by primary care and hospital SOC after hospital discharge for diabetic limb salvage (DLS):
    a. No coordinated care exists between primary and tertiary care for patients who require wound care after hospital discharge.
    b. This results in high clinic nonattendance rates, leading to grave limb salvage consequences when wound deterioration is not expediently identified.
3. Wound imaging ecosystem:
    a. There is no healthcare cluster-wide wound imaging system to serially document a patient's wound status within our EMRs.
4. Workforce limitations:
    a. There is no care coordination for patients co-managed by primary and tertiary care sites.
    b. There is a severe lack of podiatrists in Singapore to support diabetic foot care.

In addition, DFW conducted an anonymized online poll during a teleconference continuing medical education session held on 17 June 2020, among primary care diabetic foot wound care providers, comprising doctors, nurses, and podiatrists (n = 138). Results from the survey showed that opinions on the ease of referral from primary to tertiary care were equivocal (56% responses positive or strongly positive), with concerns of care coordination from tertiary care back to primary care for co-management of DFU wounds (54% responses neutral or negative) (Figure 8).

Based on the qualitative findings from the DFW discussions and quantitative findings from the poll, we mapped out the current healthcare ecosystem for patients with DFUs (Figure 9) with the associated care gaps. In addition, we referenced existing guidelines [30,47] and best-practice DFU-related health service literature [48-52] to review our inputs and processes with resultant outputs, outcomes, and impacts. Figure 10 details the program logic of the proposed diabetic foot in primary and tertiary (DEFINITE) Care, which involved more collaborators within the healthcare cluster (n = 55) (Table 11) and adopted a tailored institution specific DFU program for scaling up across the cluster's diabetic foot ecosystem (Figure 11). Figure 12 was crafted by DEFINITE hospital Co-Lead Dr LHL and depicts a detailed description for DM foot care across the healthcare cluster.

Results

Methodology of health systems innovation to DEFINITE Care:

DEFINITE Care was launched in June 2020, and the program is groundbreaking locally and regionally in terms of health services innovation for DFU care coordination that spans primary and tertiary sites. DEFINITE Care aims to achieve coordinated MDT care across primary and tertiary institutions for patients with DFUs to decrease the clinical and economic burden of DFUs within our healthcare cluster. The four work plans of DEFINITE Care are as follows:

1. Scaling up existing primary care DM Foot STEP Foot Surveillance and tertiary care MDT-style LEAPP clinics.
2. Closed-loop coordination of care between primary and tertiary institutions.
3. Trial of a patient-centric and patient-owned digital wound imaging application.
4. Health economics analysis to evaluate the long-term financial sustainability of the program.

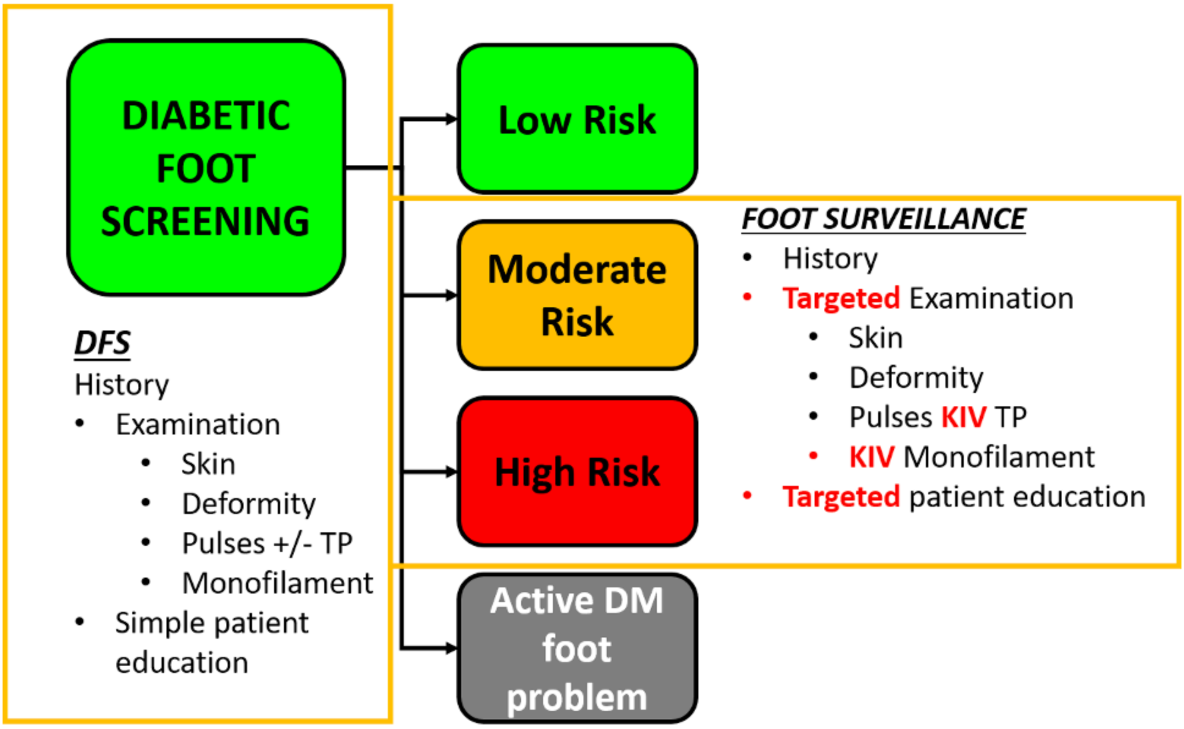
At the primary care level, DFS and FS were scaled up from two NHG to all seven NHG polyclinics (Figure 11). The roles of DFS and FS involve early identification, early treatment, and rapid referral of patients with DFUs and collaboration with hospital-based LEAPP clinics. At the tertiary care level, we scaled up existing LEAPP clinic services (MDT approach consisting of vascular surgery, endocrinology [with diabetic nurse educators], podiatry, and wound care nurses, with regular inputs from orthopedic surgery) across both hospitals, with key interventions including early access, optimization of glycemic control and medical risk factors, prompt revascularization, active wound care, appropriate offloading, and patient education (Figure 12). DEFINITE Care introduced a new workforce role—diabetic foot coordinator (DFC) (Table 11, Figure 12). Four DFCs were deployed across primary and tertiary institutions to integrate and coordinate patient care across polyclinics and hospitals. Their role includes ensuring patient adherence, tracking primary care, inpatient services, and SOC outcomes. In addition, three new podiatry posts have been added across primary and tertiary institutions in the healthcare cluster to supplement existing podiatry services and allow for the integration of DFS and FS services with the LEAPP rapid access MDT clinics. From primary to tertiary institutions across the healthcare cluster, DEFINITE Care involved more than 55 HCPs *via* an interinstitutional and multidisciplinary collaborative fashion, which was further enhanced with two monthly clinical review meetings (n = 20, from July 2020 to June 2023) and quarterly DFU-related journal clubs (n = 14, from August 2020 to July 2023). Through these meetings, we provided DFU-related HCPs with specialty-specific IWGDF guidelines [30] and a standardized health DFU memo (Appendix 2). Hence, FS may be instituted for these high-risk patients. The team was recognized nationally with the award of the Singapore National Healthcare Innovation and Productivity Medal (Care Redesign) in 2022 [53].

Table 11: Diabetic Foot Workgroup members (shaded, *n* = 19) and DEFINITE Care collaborators (*n* = 55) within the healthcare cluster.

Primary care (seven polyclinics)	Tertiary care hospital (1,700 beds)	Tertiary care hospital (800 beds)	Upcoming hospital (1,800 beds)	Administrators
Dr. ET (DFW Lead, Primary Care Lead, and Family Physician)	**Dr. SC (Hospital Lead and Vascular Surgery)**	**Dr. DO (Hospital Lead and Vascular Surgery)**	**Dr. Joseph Lo (DEFINITE Lead and Vascular Surgery)**	**Secretariat**
Family Physician A	**Dr. LHL (Hospital Co-Lead and Endocrinology)**	**Endocrinology A**	**Dr. HWH (Hospital Lead and Endocrinology)**	**Assistant Secretariat**
Family Physician B	Vascular Surgery A	Endocrinology B	Endocrinology A	**Data Analyst A**
Family Physician C	Vascular Surgery B	**Orthopedics A**	Orthopedics	Data Analyst B
Family Physician D	Vascular Surgery C	Orthopedics B	Vascular Surgery A	Data Analyst C
Nurse Sister A	Orthopedics	Vascular Surgery A	**Podiatry**	Health Economist
Nurse Sister B	**Podiatry A**	Vascular Surgery B		
Podiatry	Podiatry B	**Podiatry A**		
Individual polyclinic lead doctors (×7)	Diabetic Foot Coordinator	Podiatry B		
Individual polyclinic lead nurses (×7)		Diabetic Foot Coordinator		
Diabetic Foot Coordinator A				
Diabetic Foot Coordinator B				

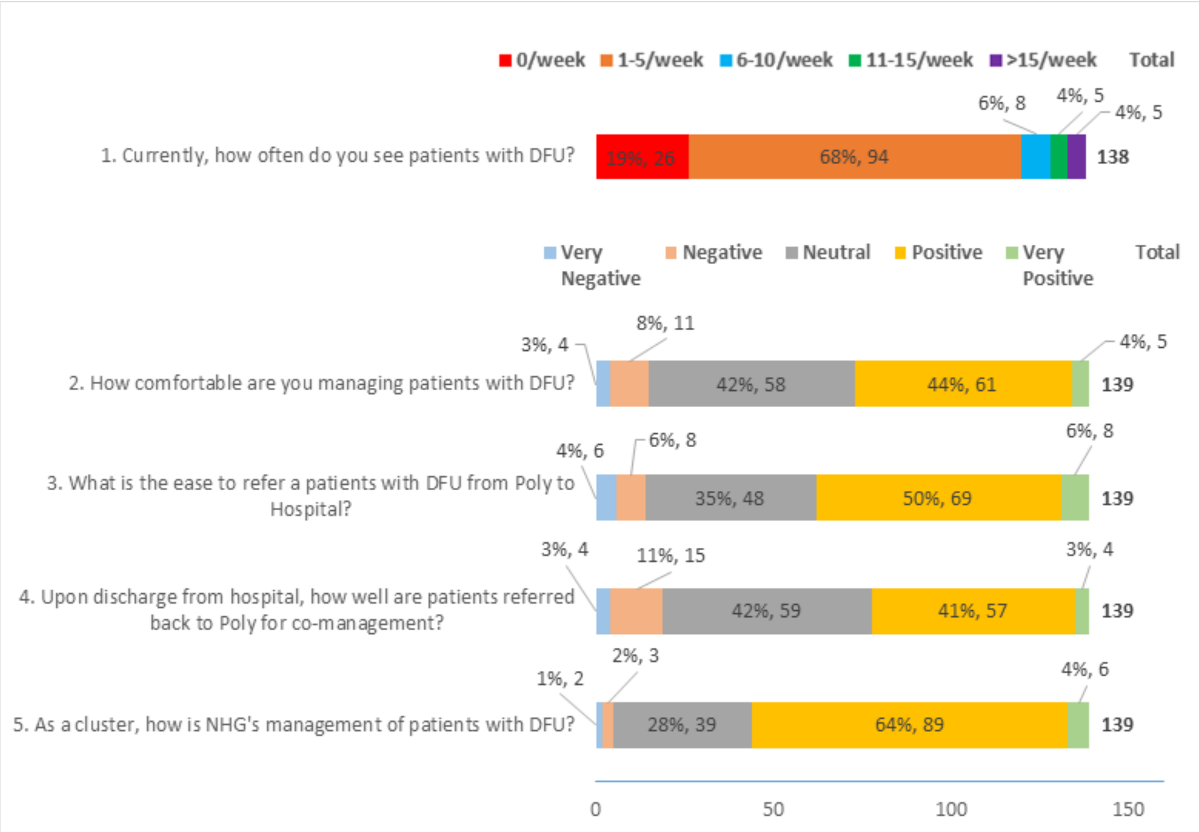
Abbreviations: DEFINITE: diabetic foot in primary and tertiary; DFW: diabetic foot workgroup

Figure 7: Primary Care DM Foot Screening and Surveillance, Treatment, Escalation Program (DM Foot STEP).



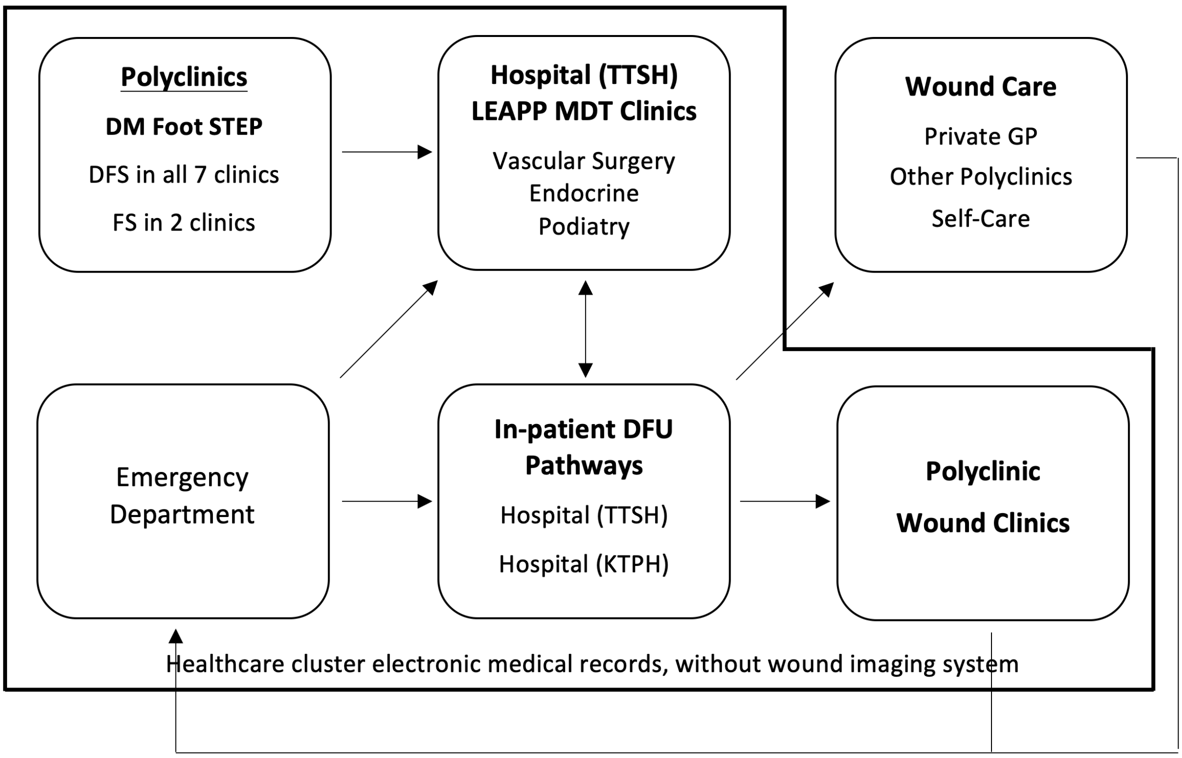
Abbreviations: DFS: diabetic foot screening; DM: diabetes mellitus; KIV: keep in view; TP: toe pressure

Figure 8: Anonymized online poll (June 17, 2020) results among primary care diabetic foot wound care providers (doctors, nurses, and podiatrists, *n* = 138) on their views regarding current DFU care within the healthcare cluster.



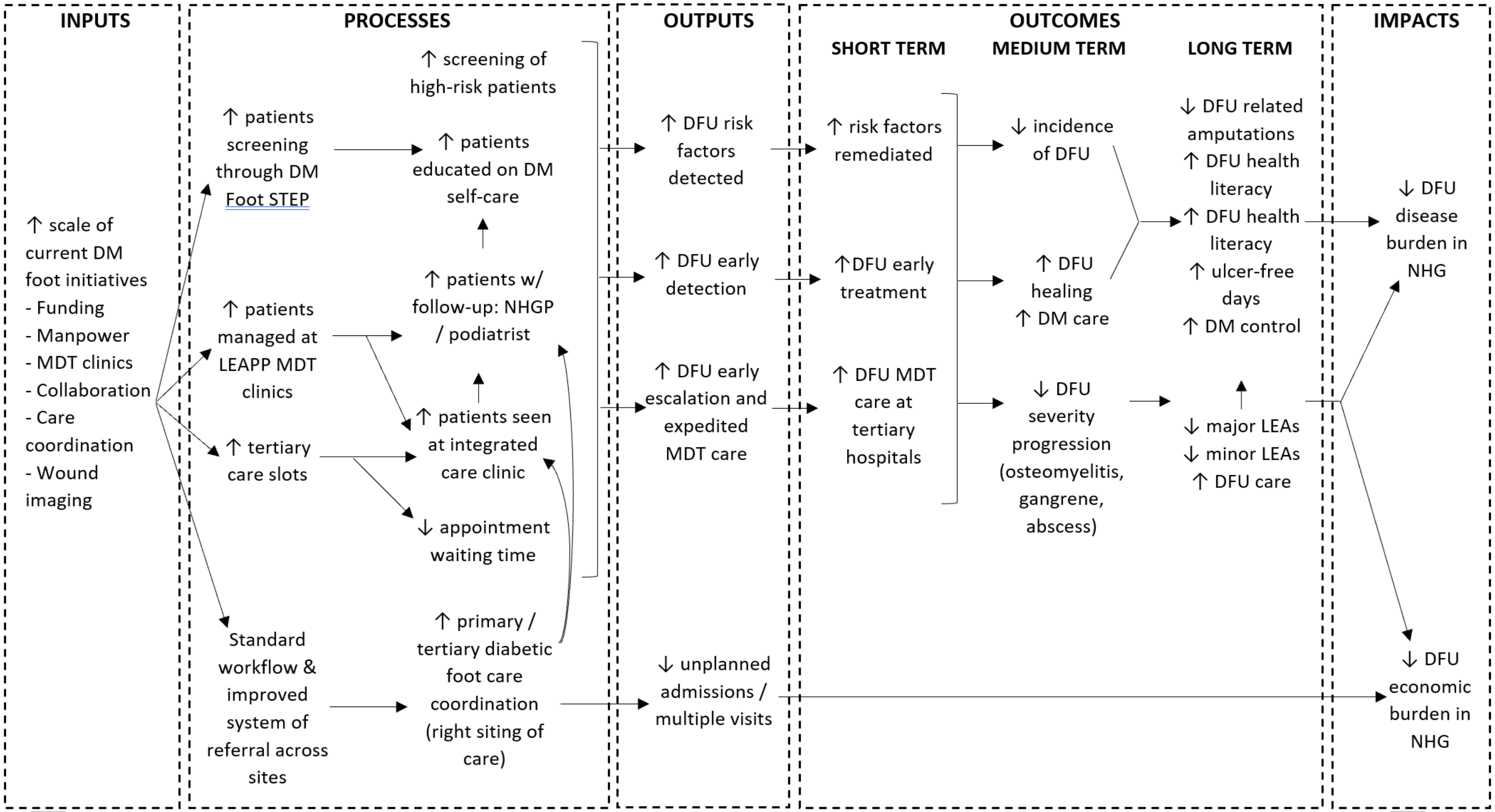
Abbreviations: DFU: diabetic foot ulcer; NHG: National Healthcare Group (our healthcare cluster comprising seven primary care polyclinics and two tertiary hospitals).

Figure 9: Pre-DEFINITE healthcare ecosystem for patients with DFUs.



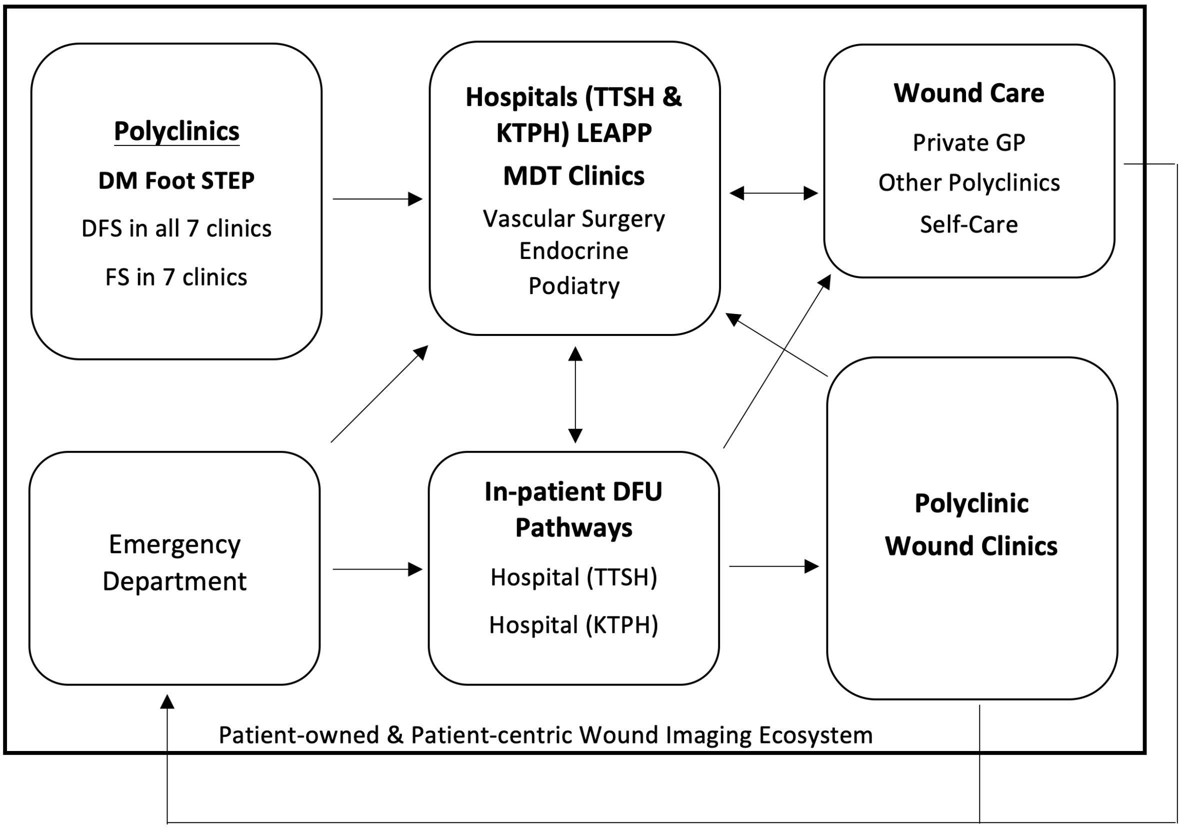
Abbreviations: DEFINITE: diabetic foot in primary and tertiary; DFS: diabetic foot screening; DFU: diabetic foot ulcer; GP: general practitioner; KTPH: Khoo Teck Puat Hospital; LEAPP: lower extremity amputation prevention program; MDT: multidisciplinary team; STEP: screening & surveillance, treatment, and escalation program; TTSH: Tan Tock Seng Hospital.

Figure 10: DEFINITE Care program logic.



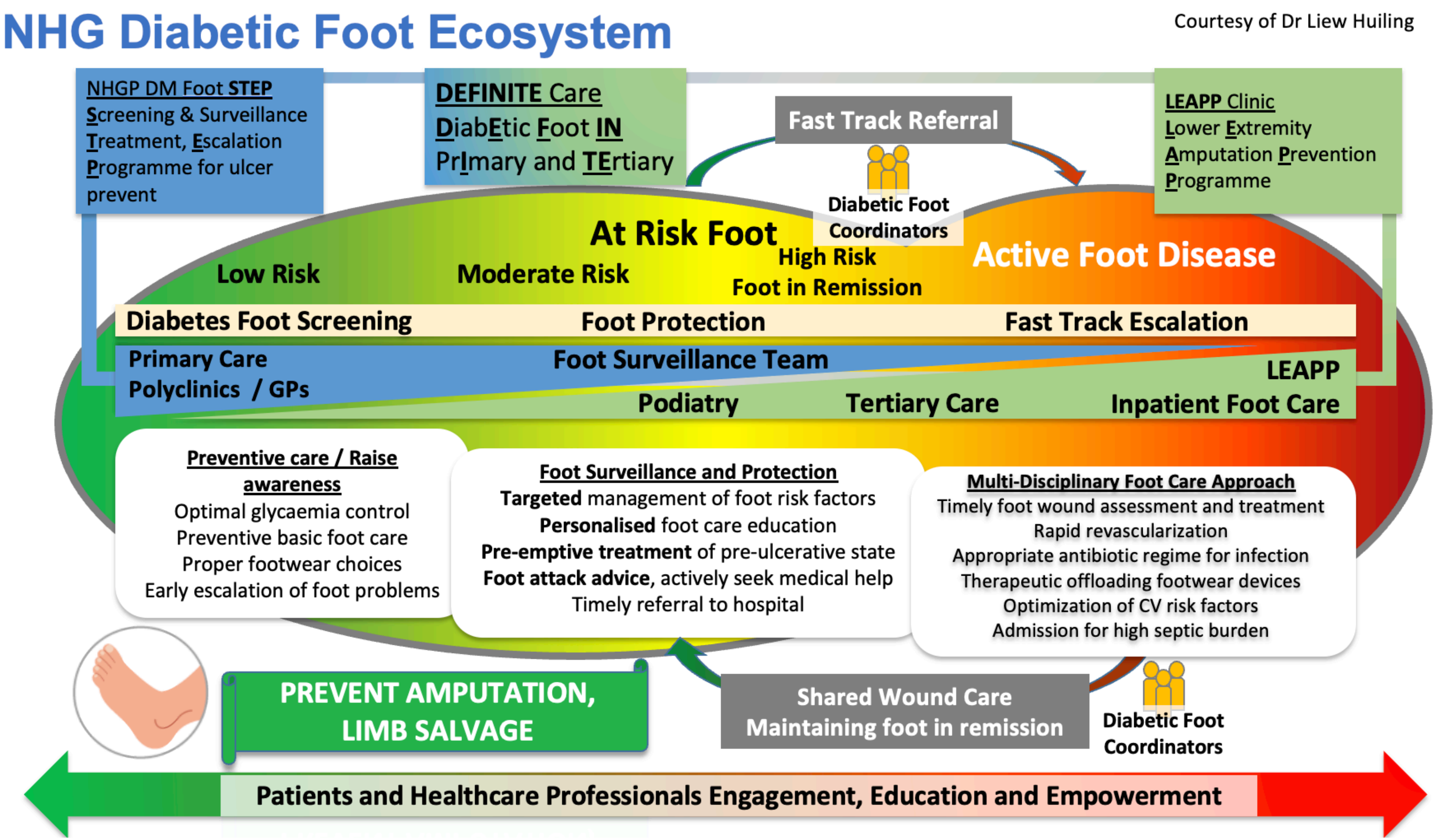
Abbreviations: DEFINITE: diabetic foot in primary and tertiary; DFU: diabetic foot ulcer; DM: diabetes mellitus; LEAPP: lower extremity amputation prevention program; MDT: multidisciplinary team; NHGP: National Healthcare Group Polyclinics; STEP: screening & surveillance, treatment, and escalation program.

Figure 11: Post-DEFINITE healthcare ecosystem for patients with DFUs.



Abbreviations: DEFINITE: diabetic foot in primary and tertiary; DFS: diabetic foot screening; DFU: diabetic foot ulcer; GP: general practitioner; KTPH: Khoo Teck Puat Hospital; LEAPP: lower extremity amputation prevention program; MDT: multidisciplinary team; STEP: screening & surveillance, treatment, and escalation program; TTSH: Tan Tock Seng Hospital.

Figure 12: Overall ecosystem for patients with diabetic foot disease.



Chapter 5: DEFINITE Care Cohort (2020–2022)

Summary

DEFINITE Care is an inter-institutional and multi-disciplinary health systems innovation program at a healthcare cluster in Singapore. This program aims to achieve coordinated MDT care across primary and tertiary care for patients with DFUs within our public healthcare cluster—an integrated network of seven primary care polyclinics and two acute care tertiary hospitals (1,700 and 800 beds) with a total catchment population of 2.2 million residents. From June 2020 to September 2022, there were 4,660 unique patients with DFUs with a mean age of 65.9 years. Among them, 61.2% were male. The mean baseline HbA1c level was 8.3%, and the mean diabetes duration was 13.3 years. In addition, the mean diabetes complication severity index (DCSI) was 5.6, and the mean Charlson Comorbidity Index (CCI) was 6.8. In the 12 months preceding enrollment in DEFINITE Care, 35.5% of patients underwent surgical foot debridement, 21.2% had minor LEA, 7.5% had major LEA, and 16.8% had revascularization procedures. Multivariate analysis revealed a history of minor amputation in the preceding 12 months as an independent predictor of major and minor amputations (HR of 3.4 and 1.8, respectively, $P < 0.001$).

Methodology

We conducted an observational population health cohort study following the STROBE guidelines [45]. Since June 2020, all patients who present with DFUs (at their first presentation) to primary care polyclinics, tertiary care LEAPP clinics, and DFU-related inpatient admissions have been recruited within DEFINITE Care. DFUs are patients with DM and tissue loss (anatomically at or distal to malleolus): ulcer/gangrene/abscess/osteomyelitis/cellulitis with or without neuroarthropathy. The exclusion criteria included patients with DM but with ulcers proximal to the malleolus (mixed arteriovenous etiology), patients with callus only, cellulitis only, PAD without tissue loss, and prediabetes. This study was approved by the institution's ethics review board (National Healthcare Group Domain Specific Review Board 2021/01154).

Follow-up data on prospective clinical, administrative, and direct healthcare costs were captured within the healthcare cluster's chronic disease management registry for diabetes, with relevant ICD9 and ICD10 diagnosis, surgical procedure, and service codes (Appendix 1). Clinical variables included demographic data, baseline comorbidities, cardiovascular profile, and DFU-related procedures (including data 12 months before recruitment in the DEFINITE Care program). The outcomes encompassed LEA (minor and major) and survival (amputation-free and all-cause) rates. In addition, the administrative variables included health service utilization at primary and tertiary care (ED attendance, inpatient admissions, LOS, readmissions, clinic visits, surgical procedures, and DFS). Direct healthcare costs were calculated from a patient's perspective (before government subsidies), including physician fees, inpatient hospital stay, procedures, supportive dressings, and adjuvant therapy. Indirect healthcare costs were not evaluated. Singapore's healthcare system adopted a mixed financing system, whereby healthcare subsidies were derived from nationalized life insurance schemes and deductions from the compulsory savings plan *via* the Central Provident Fund [41].

Moreover, a stepwise Cox-PH model was performed to identify independent predictors of major and minor LEAs. The significance level was predetermined at $P < 0.05$ for all tests. All statistical analyses were performed using Microsoft Excel 2016 (Microsoft, Redmond, Washington) and R software version 3.6.1 (R Foundation, Vienna, Austria).

Results

From June 2020 to September 2022, 4,660 unique patients with DFUs were identified within DEFINITE Care. Among them, 50.8% were managed at hospitals, 22.8% were managed at primary care, and 26.3% were comanaged between primary care and hospitals (Figure 13). The mean age was 65.9 years (SD 12.9). 61.2% of patients were male, and 20.8% were smokers or ex-smokers. The mean body mass index (BMI) was 27.0 kg/m^2 (SD 5.6), the mean baseline HbA1c level was 8.3% (SD 2.1), the mean diabetes duration was 13.3 years (SD 8.8), and the DCSI was 5.6 (SD 2.7) (Table 12). In terms of comorbidities, 85.4% had hypertension, 91.9% hyperlipidemia, 32.5% IHD, 42.5% DM retinopathy, and 19.7% ESRF, with a mean serum creatinine of 197 µmol/L (SD 222) and mean CCI of 6.8 (SD 3.1).

Regarding DFU-related procedures 12 months before enrollment to DEFINITE Care, 35.5% of patients underwent surgical foot debridement, 21.2% had minor LEA, 7.5% underwent major LEA, and 16.8% had revascularization procedures. In terms of health service utilization in the 12 months preceding enrollment into DEFINITE Care, only 31.2% had DFS despite a mean number of primary care polyclinic visits of 8.0 (SD 14.2), hospital SOC visits of 9.9 (SD 12.3), and podiatry visits of 2.4 (SD 4.4). The mean number of inpatient admissions was 1.0 (SD 1.6), with a mean cumulative DFU-related LOS of 10.0 days (SD 22.0). In the 12 months preceding enrollment into DEFINITE Care, the mean DFU-related gross direct healthcare cost per year was US$11,468 (SG$19,665).

Within the DEFINITE Care study population, compared with data from the preceding 12 months in the same cohort, a significant improvement was observed in the cardiovascular profile (glycemic and lipid control) with improved mean HbA1c (7.9% from 8.4%, $P < 0.001$), low-density lipoprotein (LDL) levels (2.1 mmol/L from 2.2, $P < 0.001$), total cholesterol

(3.9 mmol/L from 4.1, $P < 0.001$), and triglyceride levels (1.6 mmol/L from 1.8, $P = 0.002$) (Table 13). Multivariate analysis of baseline characteristics considered minor amputations in the preceding 12 months as an independent predictor of major and minor amputations (HR of 3.4 and 1.8, respectively, $P < 0.001$) (Table 14).

Table 12: DEFINITE Care baseline patient characteristics

Baseline characteristics	DEFINITE Care (Jun 2020–Sept 2022) (*n* = 4,660)
Site of diabetic foot ulcer management, *n* (%)	
Primary care only	1,076 (23.1)
Tertiary care only	2,344 (50.3)
Comanaged between primary and tertiary care	1,240 (26.6)
Mean age in years (SD)	65.9 (12.9)
Gender	
Male, *n* (%)	2,852 (61.2)
Ethnicity, *n* (%)	
Chinese	2,582 (55.4)
Malay	844 (18.1)
Indian	848 (18.2)
Smoking, *n* (%)	
Ex-smoker	480 (10.3)
Smoker	489 (10.5)
Nonsmoker	1,990 (42.7)
Physical parameters	
Mean body mass index, kg/m^2 (SD)	27.0 (5.6)
Mean systolic blood pressure, mmHg (SD)	137 (20)
Biochemistry (preceding 12 months)	
Mean serum creatinine, µmol/L (SD)	197 (222)
Mean low-density lipoproteins, mmol/L (SD)	2.2 (1.0)
Mean total cholesterol, mmol/L (SD)	4.1 (1.2)
Mean HbA1c, % (SD)	8.3 (2.1)
Comorbidities, *n* (%)	
Hypertension	3,980 (85.4)
Hyperlipidemia	4,283 (91.9)
Ischemic heart disease	1,515 (32.5)
Previous stroke	163 (3.5)
End-stage renal failure	918 (19.7)
Diabetic retinopathy	1,980 (42.5)
Charlson Comorbidity Index (SD)	6.8 (3.1)

Type 1 diabetes mellitus	224 (4.8)
Type 2 diabetes mellitus	4,436 (95.2)
Mean diabetes duration in years (SD)	13.3 (8.8)
Mean diabetes complication severity index (SD)	5.6 (2.7)
DFU-related procedures (preceding 12 months)	
Foot surgical debridement, *n* (%)	1,654 (35.5)
Minor LEA, *n* (%)	988 (21.2)
Major LEA, *n* (%)	350 (7.5)
Revascularization, *n* (%)	783 (16.8)
Health service utilization (preceding 12 months)	
Diabetic foot screening (DFS), *n* (%)	1,454 (31.2)
Mean no. of polyclinic visits (SD)	8.0 (14.2)
Mean no. of hospital specialist visits (SD)	9.9 (12.3)
Mean no. of podiatry visits (SD)	2.4 (4.4)
Mean no. of elective day surgery procedures (SD)	0.3 (1.2)
Mean no. of emergency department (ED) visits (SD)	1.4 (1.9)
Mean no. of inpatient admissions (SD)	1.0 (1.6)
Mean cumulative DFU-related length of stay, days (SD)	10.0 (22.0)
Mean DFU-related gross direct costs per year, US$ (SG$)	11,468 (19,665)

Abbreviations: DEFINITE: diabetic foot in primary and tertiary; DFU: diabetic foot ulcer; N/A: not available; SD: standard deviation; SG: Singapore; US: United States.

Table 13: DEFINITE Care 18-month cardiovascular control outcomes compared with the preceding 12 months.

Outcomes (95% CI)	**Pre-DEFINITE Care**	**Post-DEFINITE Care**	***P* value**
Mean HbA1c, % (*n* = 2,083)	8.4 (8.3–8.4)	7.9 (7.8–7.9)	***0.0001***
Mean systolic BP, mmHg (*n* = 1,820)	136 (135–137)	138 (137–139)	***0.0020***
Mean BMI, kg/m^2 (*n* = 1,730)	27.0 (26.7–27.2)	27.0 (26.7–27.2)	0.3040
Mean LDL, mmol/L (*n* = 1,243)	2.2 (2.2–2.3)	2.1 (2.1–2.2)	***0.0001***
Mean TC, mmol/L (*n* = 1,134)	4.1 (4.0–4.2)	3.9 (3.9–4.0)	***0.0001***
Mean TG, mmol/L (*n* = 1,134)	1.7 (1.7–1.8)	1.6 (1.6–1.7)	***0.0016***

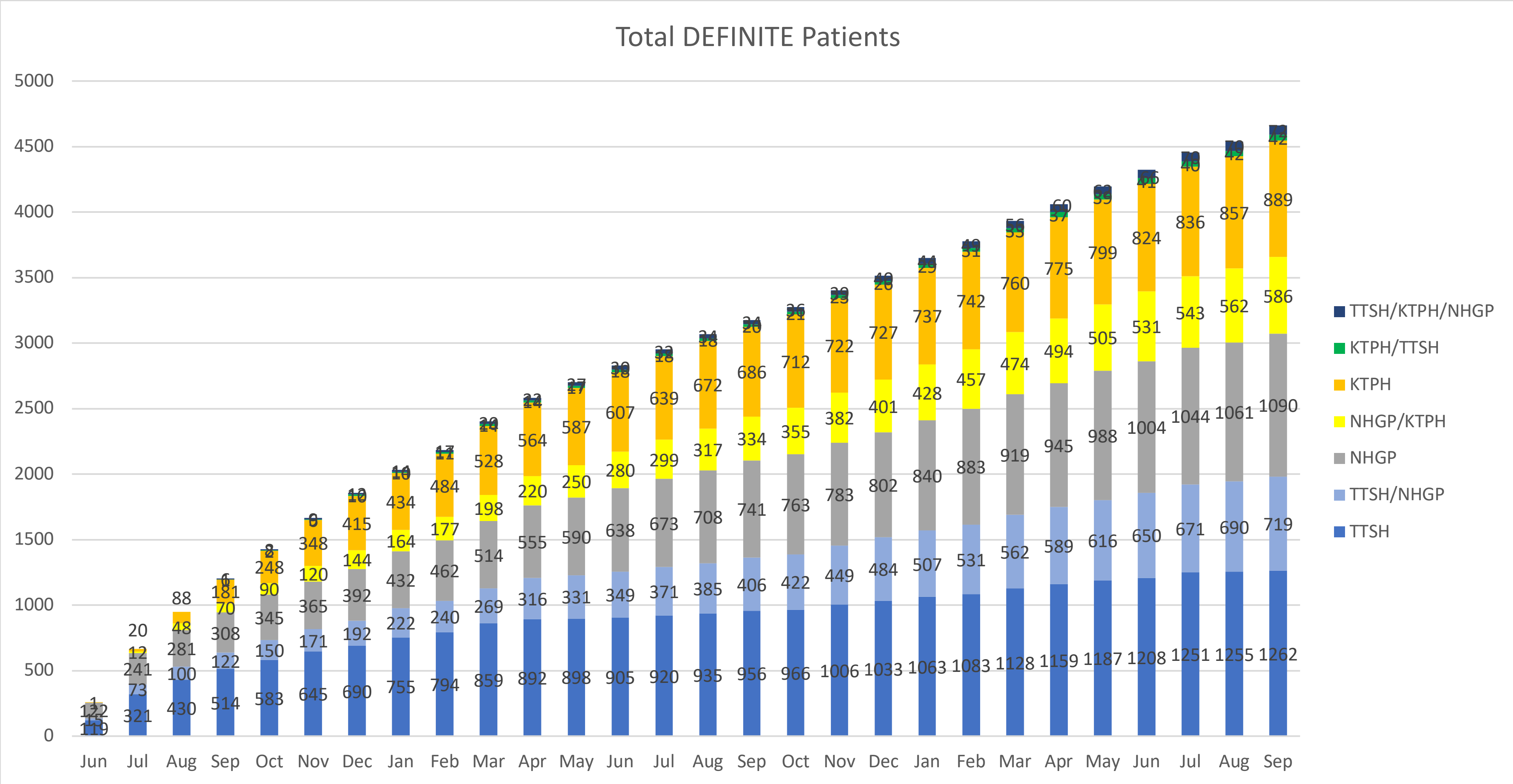
Abbreviations: BMI: body mass index; BP: blood pressure; CI: confidence interval; DEFINITE: diabetic foot in primary and tertiary; LDL: low-density lipoprotein; TC: total cholesterol; TG: triglycerides.

Table 14: Multivariate analysis on independent predictors of major and minor LEAs.

Variables	Major LEA	Minor LEA
	Hazard ratio (95% CI)	
Body mass index (kg/m^2)	0.90 (0.82–0.98) p=0.032	N/S
Systolic blood pressure (mmHg)	0.93 (0.89–0.97) p=0.045	N/S
Serum creatinine (umol/L)	1.00 (1.00–1.01) p=0.044	N/S
History of minor LEA	***3.4 (1.6–7.2)*** p<0.001	***1.8 (1.2–3.0)*** p<0.001

Abbreviations: CI: confidence interval; LEA: lower extremity amputation; N/S: not significant

Figure 13: Unique patients with DFUs recruited within DEFINITE Care (June 2020–September 2022).



DEFINITE: diabetic foot in primary and tertiary; NHGP: National Healthcare Group Polyclinics; KTPH: Khoo Teck Puat Hospital; TTSH: Tan Tock Seng Hospital

Chapter 6: Propensity Score Matching and Analysis of DEFINITE Care (2020–2022) *Versus* Control (2016–2017)

Summary

We performed 1:1 PSM on patients enrolled within DEFINITE Care (*n* = 2,798; June 2020–June 2022) against a retrospective control group (*n* = 5,462; June 2016–December 2017). At 1 year, DEFINITE had a significant 5.5% improvement in minor LEA-free survival and 9.0% improvement in major LEA-free survival with longer mean days between enrollment to minor LEA, major LEA, and death. Healthcare utilization shifted from inpatient to outpatient care, with a reduction in the mean hospital admission by 0.9 and cumulative LOS by 5.5 days. Additionally, there was a corresponding increase in primary care visits by 1.2 and hospital specialist clinic visits by 2.8. DEFINITE patients also demonstrated a significant improvement in DM control. Although DEFINITE had a net negative direct healthcare cost savings of US$1,769 (SG$2,400) per patient compared with the control group, 270 deaths were prevented, leading to cost savings of US$18,057 (SG$24,498) per death prevented. There was a significant improvement in health-related quality-of-life (HRQoL) for patients with healed DFU over a 12-month period. Within our healthcare cluster's catchment population of 2.2 million, the estimated DM-related major amputation decreased from Singapore's average of 12.1/100,000 to 8.0/100,000 population.

Methodology

This analysis compared patients enrolled within DEFINITE Care (n = 2,798, June 2020–June 2022) with a retrospective control group (n = 5,462, June 2016–December 2017) across NHG. Within both groups, patients with DFUs were defined as those with DM and tissue loss (anatomically at or distal to malleolus): ulcer/gangrene/abscess/osteomyelitis/cellulitis with or without neuroarthropathy. The exclusion criteria included patients with DM and ulcers proximal to the malleolus (mixed arteriovenous or venous etiology), callus only, cellulitis only, PAD without tissue loss, and prediabetes. All patients in both groups had a minimum of 1-year follow-up data and preceding 3-year baseline data. Patients analyzed within the DEFINITE group were excluded from the control group. The detailed methodology and patient characteristics of the DEFINITE group are described in Chapter 5, whereas those of the control group are described in Chapter 2.

PSM with replacement was employed to ensure comparability in demographics and clinical factors between the DEFINITE and control groups. PSM was performed with covariates of age, gender, race, retinopathy, IHD, CKD, ESRF, previous stroke, HbA1c, and medications (antiplatelet, anticoagulation, hypertension, statin, DM, and LEA history in the past 12 months). After PSM (1:1), a good overlap assumption was achieved. All variables exhibited a standardized mean difference of <0.1, and all variables had a low variance ratio (range 0.85–1.05) (Figure 14). The treatment effects of DEFINITE Care on minor and major LEAs, mortality, inpatient admissions, and average LOS in the subsequent 12 months were evaluated. The odds ratio (OR) of minor LEA, major LEA, and morality was evaluated, with the control cohort as the reference group, and adjusted (logistical regression) for age, gender, ethnicity, history of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, and lipid-lowering medications). The incidence rate ratio (IRR) between the DEFINITE and control groups for clinical outcomes and healthcare utilization was evaluated using Poisson regression. The control cohort served as the reference group, controlled for age, gender, ethnicity, history of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, and lipid-lowering medications). Direct healthcare costs were calculated from a patient's perspective (before government subsidies), including physician fees, inpatient hospital stay, procedures, supportive dressings, and adjuvant therapy. Indirect healthcare costs were not evaluated. Singapore's healthcare system adopted a mixed financing system, whereby healthcare subsidies were derived from nationalized life insurance schemes and deductions from the compulsory savings plan *via* the Central Provident Fund [41]. All statistical analyses were performed using Microsoft Excel 2016 (Microsoft, Redmond, Washington) and R software version 3.6.1 (R Foundation, Vienna, Austria).

In addition, we evaluated health-related quality-of-life (HRQoL) parameters using EuroQol EQ5D and Diabetic Foot Ulcer Scale Short Form (DFS-SF) (Figure 16). EQ5D and DFS-SF questionnaires were administered by trained diabetic foot coordinators over phone, on recruitment (first presentation of DFU) and subsequently at 3, 6, 9 and 12 months. EQ5D (Appendix 3) is a generic measure of HRQoL and has five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [54]. Each domain has 5 response options, including no problems, slight problems, moderate problems, severe problems and extreme problems. The scores obtained were attached to an EQ5D profile according to a set of weights based on data from the United States, with values anchored at 0 (a state as bad as being dead) and 1 (full health). A sixth question (EQ6) assessed perceived health on a scale of 0 to 100, where 100 represents the best health they can imagine and thus a better HRQoL. DFS-SF (Appendix 4) is a disease-specific patient-reported outcomes measure (PROM) instrument that measures specific factors impacting patients' lives as a result of their DFU [55]. The following six conceptual domains are evaluated: leisure, physical health, dependence/daily life, negative emotions, worried about ulcers/feet and bothered by ulcer care. Each item has 5 response options from 1 to 5. All DFS scales are then scored from 0 to 100 after reverse-coding the responses, with higher scores indicating a better HRQoL. The scores are added up to give a total score ranging from 29 to 145.

Results

Between June 2016 and December 2017, 5,462 patients presented with DFUs within the control group. However, from June 2020 to June 2022, 2,798 patients presented with DFUs within the DEFINITE group (Table 15). After 1:1 PSM, 2,798 patients were included in each group. Compared to the control group, the DEFINITE cohort had significantly fewer nonsmokers (42.5% *vs*. 54.8%), more history of minor LEA in the past 3 years (8.8% *vs*. 4.2%), smokers/ex-smokers (21.1% *vs*. 28.3%), and lower mean CCI (2.8 *vs*. 3.4). All other variables were similar between both groups after PSM.

DEFINITE patients showed a significantly lower mortality rate at 1 year (14.3% *vs*. 30.7%), with resultant lower minor LEA/death rates (24.1% *vs*. 29.0%) and lower major LEA/death rates (18.8% *vs*. 27.8%) (Table 16). ORs for death, minor LEA/death, and major LEA/death were 0.48, 0.73, and 0.57, respectively ($P < 0.001$) (Table 17). Correspondingly, DEFINITE patients had longer mean days between enrollment and first minor LEA (68.3 *vs*. 56.7 days), longer mean days between enrollment and major LEA (99.1 *vs*. 82.6 days), and longer mean days between enrollment and death (163.3 *vs*. 118.6 days). IRRs for days from enrollment to minor LEA, major LEA, and death were 1.08, 1.15, and 1.40, respectively ($P < 0.001$) (Table 18). Within our healthcare cluster's catchment population of 2.2 million, the estimated DM-related major amputation decreased from Singapore's average of 12.1/100,000 to 8.0/100,000 population, as compared to the OECD average of 6.4/100,000 population [39].

In terms of healthcare utilization, DEFINITE patients had fewer inpatient admissions (1.6 *vs*. 2.5 episodes), fewer ED visits (1.5 *vs*. 2.7 episodes), and shorter cumulative LOS (18.1 *vs*. 23.6 days) (Table 19). IRRs for inpatient admissions, ED visits, and cumulative LOS were 0.57, 0.55, and 0.78, respectively ($P < 0.001$) (Table 18). Correspondingly, a significant amount of outpatient resource utilization was noted, with more primary care polyclinic visits (3.0 *vs*. 1.8 episodes) and more hospital SOC visits (5.6 *vs*. 2.8 episodes). IRRs for polyclinic and SOC visits were 1.55 and 2.30, respectively ($P < 0.001$) (Table 18).

After using a mixed-effect random intercept model, DEFINITE patients showed an improved cardiovascular profile at 24 months, with significant improvement in mean HbA1c from 8.03% to 7.85% compared with 7.72% to 7.52% in the control group ($P = 0.011$) (Figure 15). Notably, the mean HbA1c of the DEFINITE group at baseline was significantly higher than that of the control cohort (8.03 *vs*. 7.72, $P < 0.001$). A statistically insignificant improvement was observed in mean LDL from 2.15 to 2.11 compared with 2.32 to 2.13 in the control group ($P = 0.871$). In addition, no significant improvement was noted in systolic blood pressure control or BMI.

At 1 year, the mean direct healthcare cost per patient within the DEFINITE group was US$24,288 (SG$32,952). It was US$1,682 (SG$2,282) higher than the mean cost per patient within the control group at US$22,606 (SG$30,670) (Table 20). With a total program operational cost of US$239,980 (SG$325,589), this translates to a mean program cost per patient of US$87 (SG$118). Overall, the DEFINITE group had a net negative direct healthcare cost savings of US$1,769 (SG$2,400) per patient compared with the control group. However, with 270 deaths prevented, cost savings per death prevented for DEFINITE was US$18,057 (SG$24,498).

In terms of HRQoL, the mean EQ5D utility value on DFU presentation was 0.736 ± 0.240, with median EQ6 perceived health at 65 (range 50-80) (n=147) (Table 21 and Figure 17). With DFU healing (88/147, 59.9%) there was a significant improvement in mean EQ5D utility value at 1 year (0.811 to 0.915 for healed DFU *versus* 0.788 to 0.844, p=0.005), with a corresponding improvement in median EQ6 perceived health (65 to 80 for healed DFU *versus* 70 to 73 for non-healed DFU, p=0.007) (Table 21). For PROMs QoL as measured by DFS-SF, the mean score on DFU presentation was 73.8 ± 34.0 (leisure), 84.6 ± 19.1 (physical health), 89.5 ± 20.3 (dependence/daily life), 81.0 ± 21.1 (negative emotions and worry), 85.4 ± 19.5 (bothered by ulcer care) and 82.5 ± 16.9 (total) (n=105) (Table 22 and Figure 18). Similarly, for patients with healed DFU (56/105, 53.3%), there was a significant improvement in scores across all categories (leisure, physical health, dependence/daily life, negative emotions and worry, bothered by ulcer care and total score) at 1 year.

Table 15: Profile of patients in DEFINITE and historical control cohorts before and after PSM.

	Before PSM			After PSM		
	Control (*n* = 5,462)	**DEFINITE (*n* = 2,798)**	***P* value**	**Control (*n* = 2,798)**	**DEFINITE (*n* = 2,798)**	***P* value**
Age, mean (SD)	71.6 (13.2)	65.7 (12.7)	<0.001	65.6 (13.8)	65.7 (12.7)	0.650
Gender			<0.001			0.525
Male	2,936 (53.8)	1,718 (61.4)		1,731 (61.9)	1,718 (61.4)	
Female	2,526 (46.3)	1,080 (38.6)		1,067 (38.1)	1,080 (38.6)	
Ethnicity			<0.001			0.427
Chinese	3,583 (65.6)	1,560 (55.8)		1,619 (57.9)	1,560 (55.8)	
Malay	768 (14.1)	493 (17.6)		488 (17.4)	493 (17.6)	
Indian	733 (13.4)	507 (18.1)		491 (17.6)	507 (18.1)	
Others	378 (6.9)	238 (8.5)		200 (7.2)	238 (8.5)	
Smoking status			<0.001			<0.001
Nonsmoker	3,239 (59.3)	1,190 (42.5)		1,533 (54.8)	1,190 (42.5)	
Ex-smoker	655 (12.0)	275 (9.8)		344 (12.3)	275 (9.8)	
Current smoker	582 (10.7)	317 (11.3)		448 (16.0)	317 (11.3)	
Unknown	986 (18.1)	1,016 (36.3)		474 (17.0)	1,016 (36.3)	
History of LEA						
Minor LEA in the past 3 years	164 (3.0)	247 (8.8)	<0.001	117 (4.2)	247 (8.8)	<0.001

Minor LEA in the past 1 year	54 (1.0)	57 (2.0)	<0.001	53 (1.9)	57 (2)	0.622
Major LEA in the past 3 years	129 (2.4)	81 (2.9)	0.145	74 (2.6)	81 (2.9)	0.745
Major LEA in the past 1 year	42 (0.8)	18 (0.6)	0.525	24 (0.9)	18 (0.6)	0.424
Medications						
Antiplatelet	3,230 (59.1)	1,676 (59.9)	0.203	1,620 (57.9)	1,676 (59.9)	0.678
Anticoagulant	969 (17.7)	442 (15.8)	0.026	459 (16.4)	442 (15.8)	0.367
Lipid-lowering	4,311 (78.9)	2,204 (78.8)	0.869	2,198 (78.6)	2,204 (78.8)	0.679
Antihypertensive	4,546 (83.2)	1,968 (70.3)	<0.001	1,976 (70.6)	1,968 (70.3)	0.466
Insulin	1,657 (30.3)	1,235 (44.1)	<0.001	991 (35.4)	1,235 (44.1)	<0.001
Oral DM medications	3,697 (67.7)	2,172 (77.6)	<0.001	2,102 (75.1)	2,172 (77.6)	<0.050
Type of DM medications			<0.001			<0.001
Not on DM medication	1,364 (25.0)	493 (17.6)		466 (16.7)	493 (17.6)	
Oral DM medication only	2,441 (44.7)	1,070 (38.2)		1,341 (47.9)	1,070 (38.2)	
Insulin only	401 (7.3)	133 (4.8)		230 (8.2)	133 (4.8)	
Oral DM medication and	1,256 (23)	1,102 (39.4)				
insulin				761 (27.2)	1,102 (39.4)	
HbA1c, mean (SD)	7.7 (2.1)	8.1 (2.0)	<0.001	8.1 (2.4)	8.1 (2)	0.110
Comorbidities						
CCI, mean (SD)	3.9 (2.1)	2.8 (1.7)	<0.001	3.4 (2)	2.8 (1.7)	<0.001
Hypertension	5,188 (95.0)	2,235 (79.9)	<0.001	2,476 (88.5)	2,235 (79.9)	<0.001
Dyslipidemia	5,077 (93.0)	2,259 (80.7)	<0.001	2,494 (89.1)	2,259 (80.7)	<0.001

Diabetic retinopathy	1,787 (32.7)	1,044 (37.3)	<0.001	1,007 (36)	1,044 (37.3)	0.676
Dementia	1,320 (24.2)	162 (5.8)	<0.001	420 (15)	162 (5.8)	<0.001
Ischemic heart disease	2,166 (39.7)	828 (29.6)	<0.001	886 (31.7)	828 (29.6)	0.358
History of stroke	2,058 (37.7)	487 (17.4)	<0.001	907 (16.2)	420 (15)	0.406
End-stage renal failure	1,117 (20.5)	479 (17.1)	<0.001	457 (16.3)	479 (17.1)	0.797
CKD severity			<0.001			0.647
No CKD	993 (18.2)	827 (29.6)		825 (29.5)	827 (29.6)	
Mild	1,477 (27.0)	892 (31.9)		895 (32)	892 (31.9)	
Moderate	1,695 (31.0)	642 (22.9)		644 (23)	642 (22.9)	
Severe	1,297 (23.8)	437 (15.6)		434 (15.5)	437 (15.6)	

Abbreviations: CCI: Charlson Comorbidity Index; CKD: chronic kidney disease; DEFINITE: diabetic foot in primary and tertiary; DM: diabetes mellitus; IHD: ischemic heart disease; LEA: lower extremity amputation; PSM: propensity score matching; SD: standard deviation.

Table 16: Mortality and amputation outcomes at 1 year between DEFINITE and control groups.

Outcomes (*n* = 5,512)	**At 1 year, DEFINITE group had…**	**Difference (95% CI)**	***P* value**
Mortality	Lower mortality rate	−16.4% (−14.3% to −20.7%)	**<0.001**
Minor LEA-free survival	Higher composite minor LEA-free survival	+4.9% (+2.3% to +7.6%)	**<0.001**
Major LEA-free survival	Higher composite major LEA-free survival	+9.0% (+6.4% to +11.6%)	**<0.001**
Mean days to minor LEA	Longer time to minor LEA	+11.6 (+8.3 to +36.7)	**<0.001**
Mean days to major LEA	Longer time to major LEA	+16.5 (+9.1 to +52.6)	**<0.001**
Mean days to mortality	Longer time to death	+44.7 (+33.3 to +98.6)	**<0.001**

Abbreviations: CI: confidence interval; DEFINITE: diabetic foot in primary and tertiary; LEA: lower extremity amputation.

Table 17: Adjusted 1-year risk for DEFINITE *versus* control groups.

Adjusted 1-year outcomes	**OR**	**P > z**	**95% CI**
Minor LEA	2.02	**<0.001**	1.66, 2.47
Major LEA	1.14	0.302	0.89, 1.45
Death	0.48	**<0.001**	0.41, 0.55
Composite of minor LEA/death	0.73	**<0.001**	0.64, 0.83
Composite of major LEA/death	0.57	**<0.001**	0.49, 0.65

Note: the control cohort is the reference group—adjusted (logistical regression) for age, gender, ethnicity, history of diabetic retinopathy, IHD, end-stage renal failure, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, and lipid-lowering medications)

Abbreviations: CI: confidence interval; LEA: lower extremity amputation; OR: odds ratio.

<u>Table 18: Adjusted 1-year outcomes for DEFINITE *versus* control groups.</u>

Adjusted 1-year outcomes	IRR	P > z	95% CI
Inpatient admissions	0.57	**<0.001**	0.54, 0.59
Cumulated length of stay	0.78	**<0.001**	0.78, 0.79
Emergency department visits	0.55	**<0.001**	0.53, 0.58
Primary care polyclinic visits	1.55	**<0.001**	1.5, 1.61
Hospital specialist outpatient clinic visits	2.30	**<0.001**	2.24, 2.37
Day surgery visits	1.93	**<0.001**	1.75, 2.13
Days from enrollment to minor lower extremity amputation	1.08	**<0.001**	1.05, 1.1
Days from enrollment to major lower extremity amputation	1.15	**<0.001**	1.12, 1.17
Days from enrollment to death	1.40	**<0.001**	1.38, 1.41

Note: the control cohort is the reference group—adjusted (Poisson regression) for age, gender, ethnicity, history of diabetic retinopathy, ischemic heart disease, end-stage renal failure, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, and lipid-lowering medications).

Table 19: Healthcare utilization between DEFINITE and control groups.

Study groups	Inpatient episodes	Length of stay (days)	Emergency department episodes	Day surgery episodes	Specialist clinic visits	Primary care visits
Control (n = 2,756)	2.5	23.6	2.7	0.2	2.8	1.8
DEFINITE (n = 2,756)	1.6	18.1	1.5	0.4	5.6	3.0
Difference (P < 0.001)	**−0.9**	**−5.5**	**−1.2**	**+0.2**	**+2.8**	**+1.2**

<u>Table 20: Comparison of direct healthcare costs between control and DEFINITE groups.</u>

Cohort	**Mean cost per patient, US$ (SGD$)**	**Program cost, US$ (SG$)**	**Mean program cost per patient, US$ (SG$)**	**Total cost saving per patient, US$ (SG$)**	**Deaths prevented#**	**Cost savings per death prevented*, US$ (SG$)**
Control (*n* = 2,756)	22,606 (30,670)	-	-	-	-	-
DEFINITE (*n* = 2,756)	24,288 (32,952)	239,980 (325,589)	87 (118)	**−1,769 (−2,400)**	**270**	**18,057 (24,498)**

Difference in total deaths between control and DEFINTIE cohorts (after propensity-score matching)

* Difference in total direct costs between control and DEFINITE cohorts and divided by total deaths prevented

Abbreviations: DEFINITE: diabetic foot in primary and tertiary; SG: Singapore; US: United States.

Table 21: EQ5D Utility Values and EQ6 perceived health in patients with DFU (n=147)

	EQ5D Utility Value		EQ6 (Perceived Health)	
	Mean ± SD	**p-value**	**Median (IR)**	**p-value**
Baseline	0.736 ± 0.240		65 (50 - 80)	
Month 3	0.856 ± 0.188	**<0.001**	70 (60 - 85)	**0.012**
Month 6	0.802 ± 0.248	**0.008**	70 (60 - 80)	0.107
Month 9	0.910 ± 0.161	**<0.001**	80 (70 - 85)	**<0.001**
Month 12	0.886 ± 0.188	**<0.001**	75 (64 - 85)	**0.004**
Baseline	0.811 ± 0.204		65 (50 - 85)	
Healed	0.915 ± 0.159	**<0.001**	80 (70 - 90)	**0.02**
Baseline	0.788 ± 0.204		70 (50 - 80)	
Non-healed	0.844 ± 0.192	0.032	73 (60 - 80)	0.203
Healed	0.915 ± 0.159		80 (70 - 90)	
Non-healed	0.844 ± 0.192	**0.005**	73 (60 - 80)	**0.007**

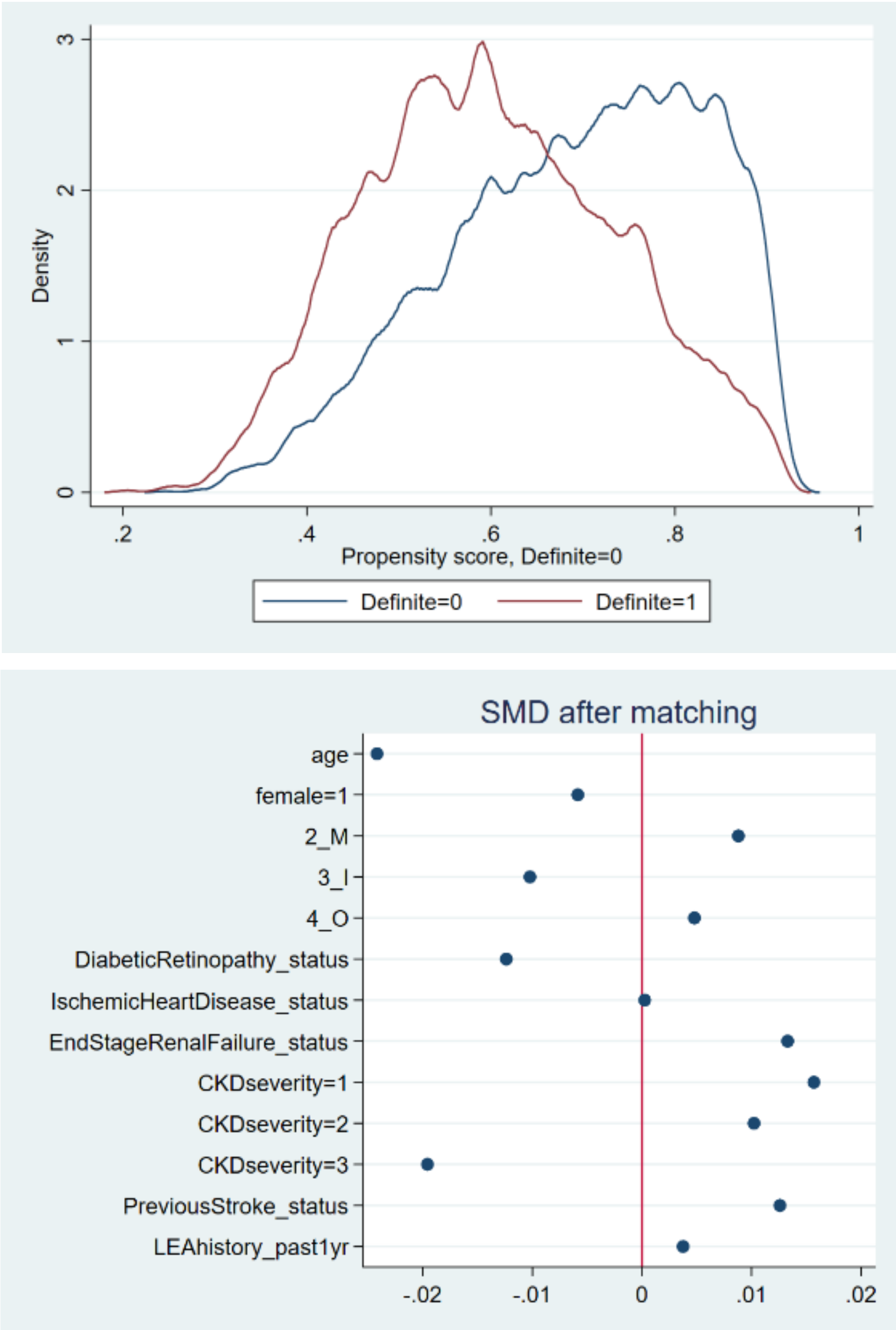
Abbreviations: DFU: diabetic foot ulcer; IR: interquartile range; SD: standard deviation

Table 22: DFS-SF domains of HRQoL in patients with DFU (n=105)

	Leisure		Physical Health		Dependence/Daily Life		Negative Emotions & Worry		Bothered by Ulcer Care		DFS-SF Total	
	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Baseline	73.8 ± 34.0		84.6 ± 19.1		89.5 ± 20.3		81.0 ± 21.1		85.4 ± 19.5		82.5 ± 16.9	
M3	81.7 ± 32.7	**0.007**	92.5 ± 12.7	**<0.001**	91.7 ± 21.2	**0.018**	84.4 ± 20.8	0.276	84.0 ± 21.3	0.979	86.5 ± 17.7	**0.002**
M6	85.3 ± 27.5	**0.003**	92.3 ± 18.5	**<0.001**	93.7 ± 14.2	**0.018**	85.7 ± 22.1	**0.033**	84.7 ± 20.8	0.868	88.0 ± 17.4	**<0.001**
M9	87.8 ± 23.3	**0.002**	96.3 ± 10.4	**<0.001**	93.7 ± 13.9	**0.028**	91.0 ± 14.5	**<0.001**	87.5 ± 17.4	0.286	91.3 ± 11.9	**<0.001**
M12	86.8 ± 24.2	**0.003**	95.5 ± 12.7	**<0.001**	95.0 ± 14.3	**0.002**	89.8 ± 17.9	**<0.001**	88.7 ± 18.3	0.117	91.0 ± 14.2	**<0.001**
Baseline	72.6 ± 34.6		86.1 ± 17.8		93.1 ± 15.7		85.3 ± 18.6		86.1 ± 16.5		84.0 ± 14.5	
Healed	87.6 ± 26.4	**0.012**	97.3 ± 11.4	**<0.001**	96.1 ±13.7	**0.024**	92.1 ± 15.5	**0.049**	95.2 ± 10.9	**<0.001**	93.3 ± 13.2	**<0.001**
Baseline	72.6 ± 33.2		85.3 ± 18.4		87.0 ± 25.1		78.2 ± 24.5		83.5 ± 20.7		80.7 ± 19.1	
Non-healed	77.4 ± 30.6	0.202	90.8 ± 17.1	**0.028**	88.4 ± 21.4	0.47	82.6 ± 21.0	0.301	77.0 ± 22.6	0.244	83.4 ± 17.4	0.113
Healed	87.6 ± 26.4		97.3 ± 11.4		96.1 ±13.7		92.1 ± 15.5		95.2 ± 10.9		93.3 ± 13.2	
Non-healed	77.4 ± 30.6	**0.05**	90.8 ± 17.1	**<0.001**	88.4 ± 21.4	**0.016**	82.6 ± 21.0	**0.001**	77.0 ± 22.6	**<0.001**	83.4 ± 17.4	**<0.001**

Abbreviations: DFS-SF: diabetic foot ulcer scale short form; DFU: diabetic foot ulcer; HRQoL: health-related quality-of-life; SD: standard deviation

Figure 14: After PSM matching, there is a good overlap assumption (A), low standardized mean difference (B), and low variance ratio (C).



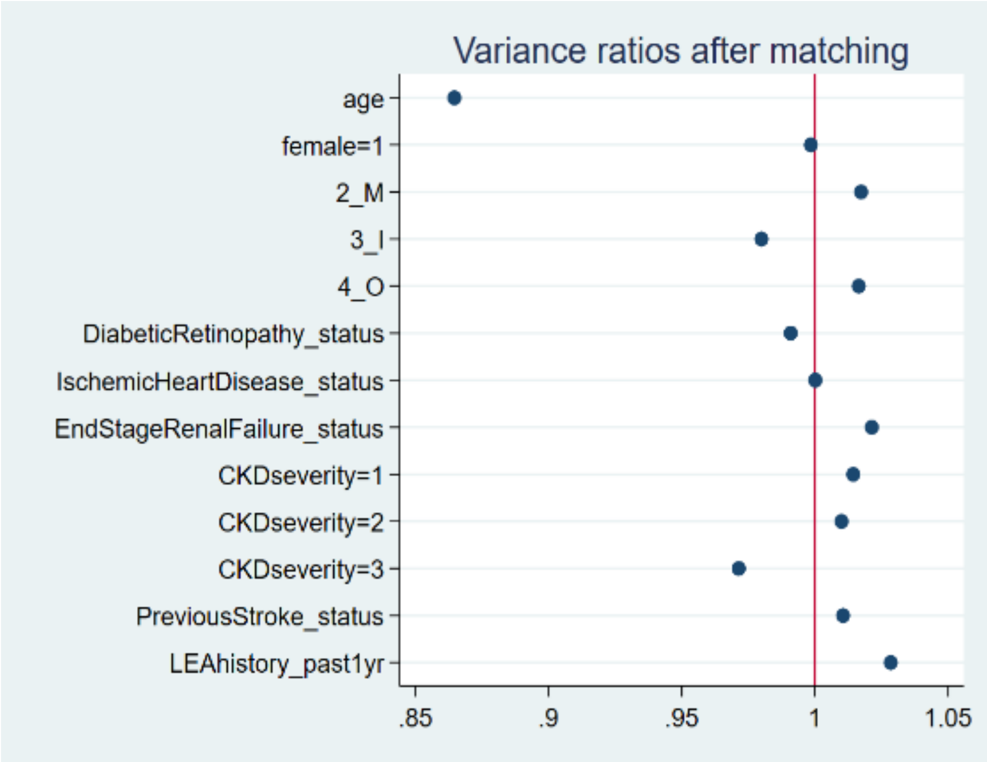
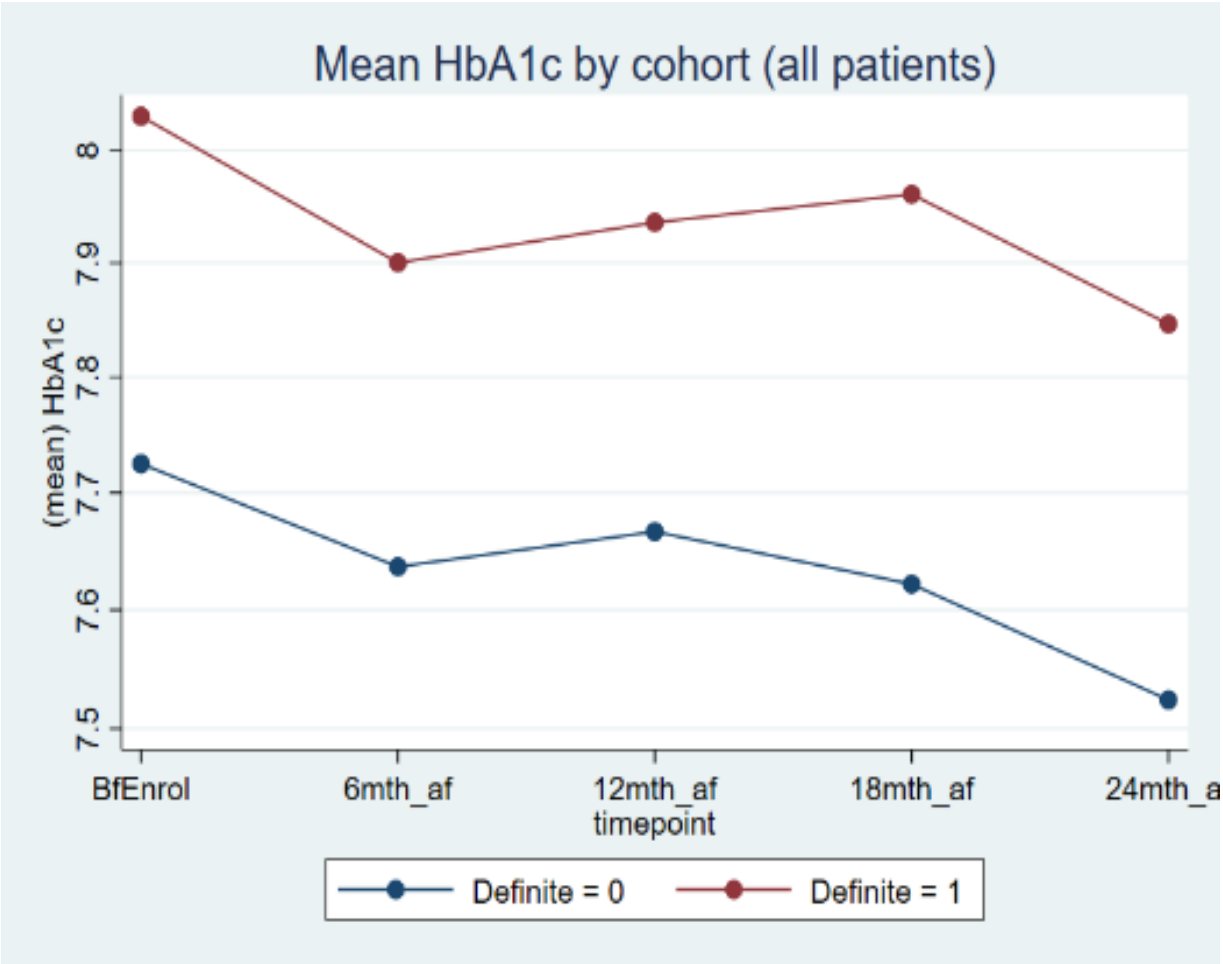

Variance ratios after matching
age
female=1
2_M
3_I
4_O
DiabeticRetinopathy_status
IschemicHeartDisease_status
EndStageRenalFailure_status
CKDseverity=1
CKDseverity=2
CKDseverity=3
PreviousStroke_status
LEAhistory_past1yr
.85
.9
.95
1
1.05

Figure 15: Mean HbA1c of the control *versus* DEFINITE groups.



HbA1c	Control			Definite			p-value
	n	Mean	SD	n	Mean	SD	
Baseline	5181	7.72	2.13	3561	8.03	2.02	**<0.001**
6-month	2467	7.64	1.87	1878	7.90	1.83	**<0.001**
12-month	2168	7.67	1.86	1299	7.94	1.74	**<0.001**
18-month	1995	7.62	1.81	820	7.96	1.84	**<0.001**
24-month	1706	7.52	1.73	209	7.85	1.68	**0.011**

Figure 16: Quality of life (EQ5D) and patient reported outcomes measure (DFS-SF) patient recruitment flowchart

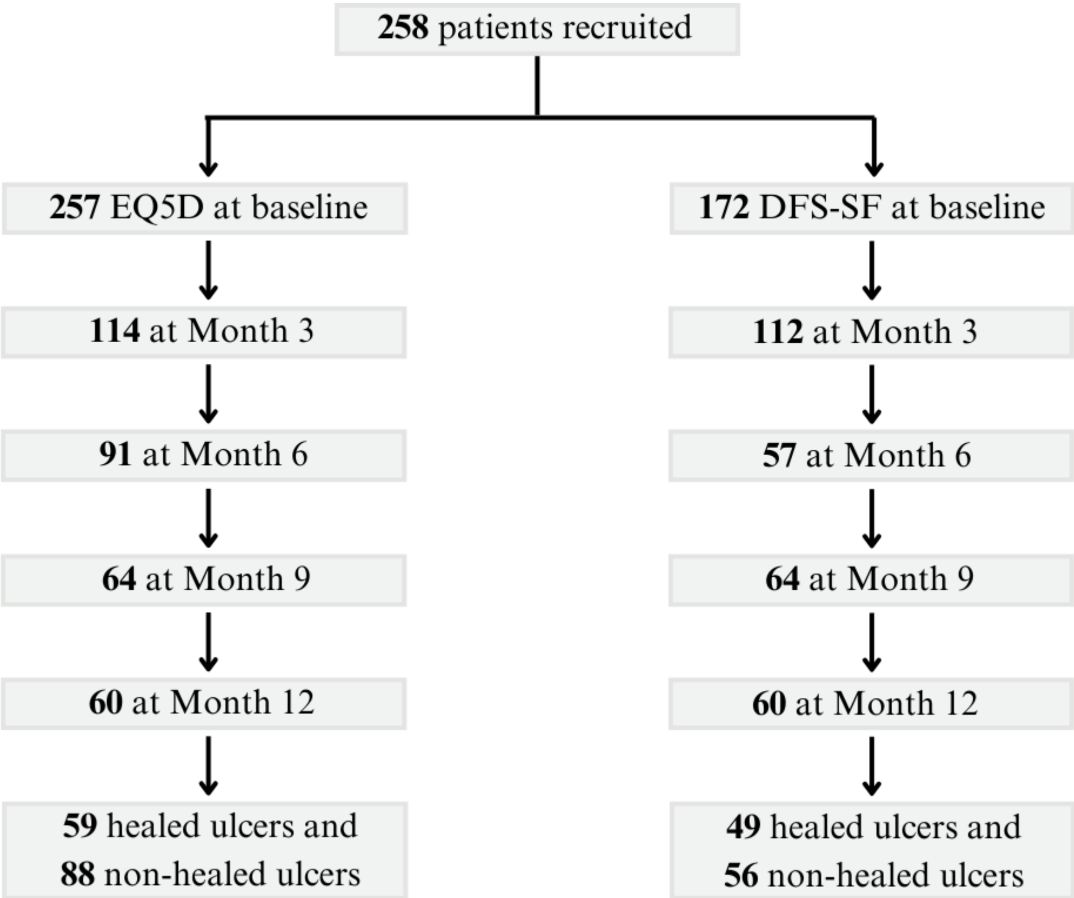
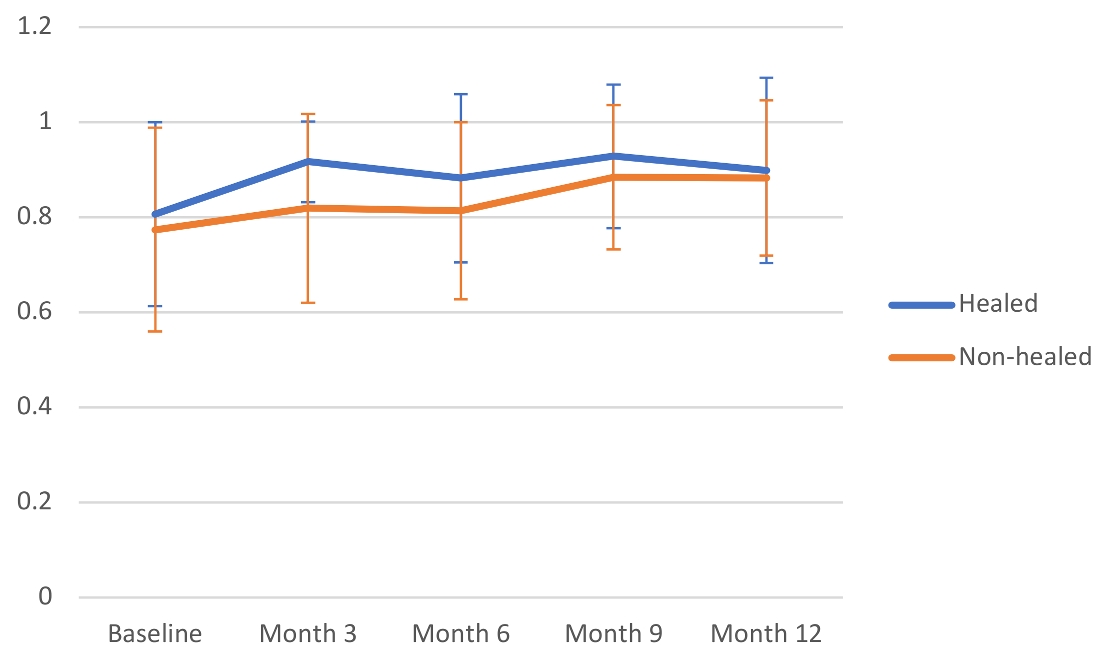


Figure 17: Quality of life EQ5D utility value (top) and EQ6 perceived health (bottom) over time



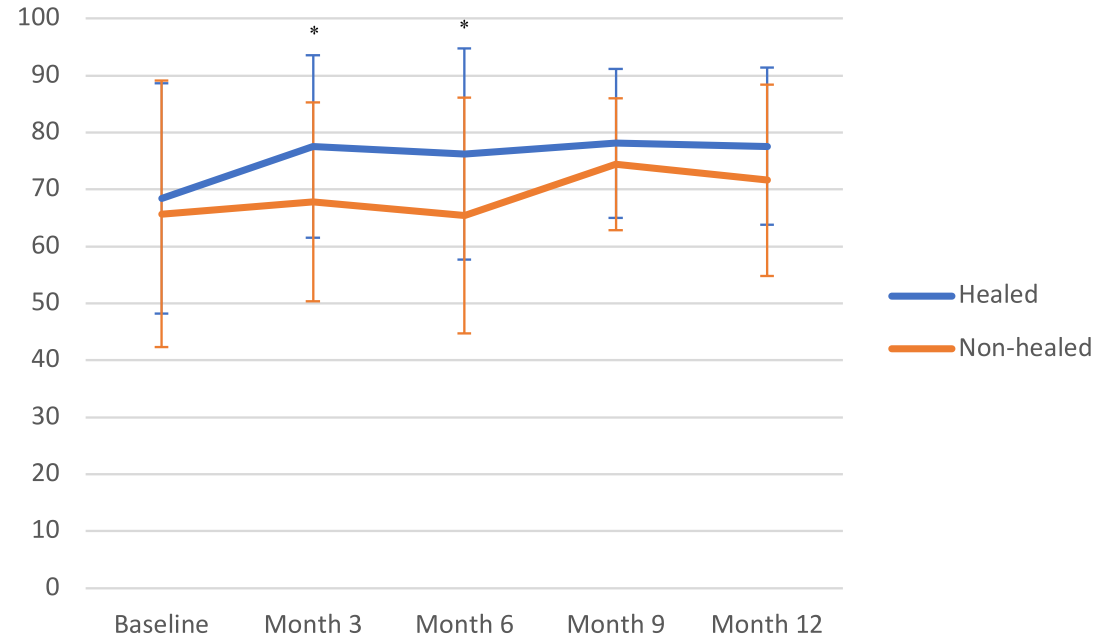
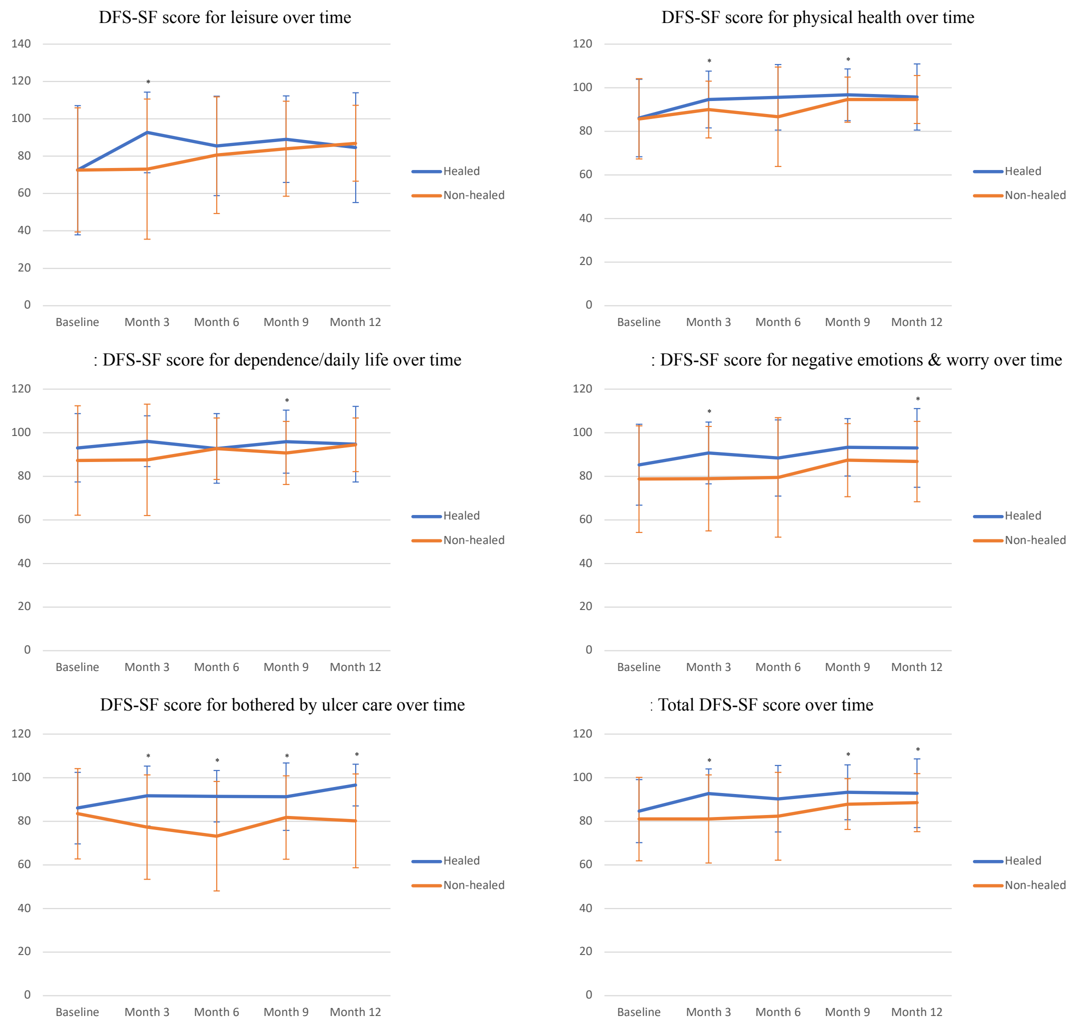


Figure 18: Patient reported outcome measures (DFS-SF) over time



Chapter 7: DEFINITE Subgroup Analysis: Characteristics and Outcomes of Patients Managed by MDT LEAPP Clinic

Summary

This part is the first of four subgroup analyses within DEFINITE Care and analyses the clinical outcomes of LEAPP and non-LEAPP patients within the program. From June 2020 to June 2022, 2,798 patients within the DEFINITE cohort completed a minimum of 12-month follow-up. Of these patients, 577 (20.6%) were managed by tertiary care MDT LEAPP clinics, whereas 2,221 = (79.4%) were non-LEAPP patients. Patients in the LEAPP cohort were older, with a higher proportion of Chinese and Indian ethnicity. In addition, they had more complications of IHD, diabetic retinopathy, and LEA in the last 1 year. After adjusting for age, gender, ethnicity, comorbidities (IHD, retinopathy, ESRF, and stroke), and medications, there was a significantly lower risk of death (OR 0.60, P = 0.001) and composite major LEA/death (OR 0.66, P = 0.002) among the LEAPP patients at 1 year with longer mean days from enrollment to minor LEA, major LEA, and death. Regarding healthcare utilization, the adjusted 1-year outcomes for LEAPP patients were an increase in inpatient admissions with an associated decrease in cumulated LOS, an increase in primary care polyclinic visits, and an increase in hospital SOC visits and elective day surgery procedures. Similar to overall DEFINITE program results, patients managed by tertiary care MDT LEAPP clinics had improved major amputation-free survival, with corresponding increase in outpatient healthcare resource utilization.

Methodology

This part is the first of four subgroup analyses within the DEFINITE Care cohort. The detailed methodology, inclusion and exclusion criteria, overall patient characteristics, and outcomes are presented in detail in Chapters 5 and 6. This chapter focuses on the tertiary care component of DEFINITE Care and evaluates clinical outcomes of LEAPP and non-LEAPP patients within the program. Since June 2020 and within DEFINITE Care, MDT LEAPP clinic services have been scaled up across both hospitals. Key interventions included early access, optimization of glycemic control and medical risk factors, prompt revascularization, active wound care, appropriate offloading, and patient education. Members of the LEAPP MDT included diabetic nurse clinicians, wound nurses, orthopedic surgeons, infectious disease physicians, prosthetics and orthotic technicians, and plastic and reconstructive surgeons who supported the team as required. Referral sources to the clinic included patients with DFUs from primary care, ED, SOCs, and inpatient wards for review after discharge. Per IWGDF guidelines [30], our MDT LEAPP clinic provided expedited access for patients with DFUs, as well as coordinated care. The inclusion criteria for the LEAPP clinic encompassed patients above 21 years who had preexisting DM and foot ulcers at or distal to the malleolus. Patients with venous ulcers or ulcers of mixed arteriovenous etiology were excluded from this analysis.

Follow-up data on prospective clinical, administrative, and direct healthcare costs were captured within the healthcare cluster's chronic disease management registry for diabetes, with relevant ICD9 and ICD10 diagnosis, surgical procedure, and service codes (Appendix 1). Factors and outcomes were evaluated using descriptive statistics. Percentages were used for categorical data, and means with SDs were used for continuous data. In addition, between-group comparisons for categorical data were performed using chi-squared tests, whereas those for continuous data were made using Student's *t*-test. All P values of <0.05 were considered statistically significant, and all *P* values were two-tailed. ORs for minor LEA, major LEA, and morality were evaluated using the non-LEAPP cohort as the reference group. They were adjusted (logistical regression) for age, gender, ethnicity, history of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, and lipid-lowering medications). The IRR between LEAPP and non-LEAPP groups for clinical outcomes and healthcare utilization was evaluated using Poisson regression. The non-LEAPP cohort was taken as the reference group. Adjustments were made for factors including age, gender, ethnicity, history of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, and lipid-lowering medications). All statistical analyses were performed using Microsoft Excel 2016 (Microsoft, Redmond, Washington) and R software version 3.6.1 (R Foundation, Vienna, Austria). This study was approved by the institution's ethics review board (National Healthcare Group Domain Specific Review Board 2021/01154).

Results

Between June 2020 and June 2022, 2,798 patients within the DEFINITE cohort completed a minimum of 12-month follow-up. Of these patients, 577 (20.6%) were managed by tertiary care MDT LEAPP clinics, whereas 2,221 (79.4%) were non-LEAPP patients. The baseline characteristics of both groups are shown in Table 23. Patients in the LEAPP cohort were older, with a mean age of 67.4 years *versus* 65.3 years in the non-LEAPP cohort ($P <$ 0.001). Furthermore, the LEAPP cohort had a higher proportion of Chinese (58.6% *vs*. 55.0%, P = 0.002) and Indians (21.3% *vs*. 17.2%, P = 0.002) than the non-LEAPP cohort. No differences were noted in gender, smoking status, mean HbA1c, or CKD status. Patients in the LEAPP cohort were more likely to have other coexisting metabolic conditions of hypertension (84.1% *vs*. 78.8%, P = 0.005) and dyslipidemia (84.6% *vs*. 79.7%, P = 0.009). Additionally, they were more likely to experience complications, such as IHD (33.6% *vs*. 28.6%, P = 0.017), stroke (19.8% *vs*. 16.8%, P = 0.049), diabetic retinopathy (41.4% *vs*. 36.2%, P = 0.022), and LEA in the last 1 year (3.8% *vs*. 2.3%, P = 0.042). No differences were observed in the history of ESRF or severity of CKD. Patients in the LEAPP cohort were more likely to be on antiplatelet (70.4% *vs*. 57.2%, P < 0.001), lipid-lowering (83.9% *vs*. 77.4%, P = 0.001), and DM (87.2% *vs*. 81.1%, P = 0.001) medications. However, they were less likely to be on anticoagulant medications (12.8% *vs*. 16.6%, P = 0.028).

For the unadjusted 1-year outcomes, LEAPP patients demonstrated significantly lower death rates (11.1% *vs*. 15.1%, P = 0.015) and composite major LEA/death (15.4% *vs*. 19.6%, p=0.021), with longer mean days from enrollment to minor LEA (99.0 *vs*. 59.1, P < 0.001), major LEA (159.0 *vs*. 84.8, P < 0.001), and death (109.1 *vs*. 112.5, P = 0.002) (Table 24). Using the non-LEAPP cohort as the reference group and after adjusting (logistical and Poisson regression) for age, gender, ethnicity, diagnosis of diabetic retinopathy, IHD (IHD), ESRF, stroke, severity of CKD, LEA in the past 1 year, and medications (antiplatelet, anticoagulant, antihypertensive, antidiabetic, and lipid-lowing), there was a significantly lower risk of death (OR 0.60, $P = 0.001$) and composite major LEA/death (OR 0.66, $P = 0.002$) among the LEAPP patients at 1 year (Table 25). Likewise, lower adjusted 1-year outcomes were noted among the LEAPP patients for mean days from enrollment to minor LEA (91.8 *vs*. 60.5 days, IRR 1.52, $P < 0.001$), major LEA (145.8 *vs*. 86.9 days, IRR 1.68, $P < 0.001$), and death (210.7 *vs*. 154.7 days, IRR 1.36, $P < 0.001$) (Table 26).

Concerning healthcare utilization, the adjusted 1-year outcomes for LEAPP patients were an increase in inpatient admissions (1.4 *vs*. 1.3, IRR 1.09, $P = 0.033$) but with an associated decrease in cumulated LOS (17.4 *vs*. 18.3 days, IRR 0.95, $P < 0.001$), an increase in primary care polyclinic visits (4.0 *vs*. 2.7, IRR 1.48, $P < 0.001$), hospital SOC visits (7.8 *vs*. 5.0, IRR 1.55, $P < 0.001$), and elective day surgery procedures (0.6 *vs*. 0.4, IRR 1.52, $P < 0.001$) (Table 26).

Table 23: Characteristics of LEAPP *versus* non-LEAPP patients.

Variables		LEAPP (*n* = 577, 20.6%)	Non-LEAPP (*n* = 2,221, 79.4%)	*P* value
Age, mean (SD)		67.4 (12.1)	65.3 (12.8)	**<0.001**
Gender				0.089
	Male	372 (64.5)	1,346 (60.6)	
	Female	205 (35.5)	875 (39.4)	
Ethnicity				**0.002**
	Chinese	338 (58.6)	1,222 (55.0)	
	Malay	77 (13.3)	416 (18.7)	
	Indian	123 (21.3)	384 (17.3)	
	Others	39 (6.8)	199 (9.0)	
Smoking status				0.555
	Nonsmoker	247 (42.8)	943 (42.5)	
	Ex-smoker	65 (11.3)	210 (9.5)	
	Current smoker	65 (11.3)	252 (11.4)	
	Unknown	200 (34.7)	816 (36.7)	
History of LEA in the past 1 year		22 (3.8)	51 (2.3)	**0.042**
Medications				
	Antiplatelet	406 (70.4)	1,270 (57.2)	**<0.001**
	Anticoagulant	74 (12.8)	368 (16.6)	**0.028**
	Lipid-lowering	484 (83.9)	1,720 (77.4)	**0.001**
	Antihypertensive	423 (73.3)	1,545 (69.6)	0.079
	DM medications	503 (87.2)	1,802 (81.1)	**0.001**
HbA1c, mean (SD)		8.0 (1.9)	8.1 (2.1)	0.644
Comorbidities				
	CCI, mean (SD)	2.8 (1.7)	2.7 (1.7)	0.318
	Hypertension	485 (84.1)	1,750 (78.8)	**0.005**
	Dyslipidemia	488 (84.6)	1,771 (79.7)	**0.009**
	Diabetic retinopathy	239 (41.4)	805 (36.2)	**0.022**
	Dementia	33 (5.7)	129 (5.8)	0.935

	Ischemic heart disease	194 (33.6)	634 (28.6)	**0.017**
	History of stroke	114 (19.8)	373 (16.8)	**0.049**
	End-stage renal failure	90 (15.6)	389 (17.5)	0.276
CKD severity				0.153
	No CKD	150 (26.0)	677 (30.5)	
	Mild	185 (32.1)	707 (31.8)	
	Moderate	144 (25.0)	498 (22.4)	
	Severe	98 (17.0)	339 (15.3)	

Abbreviations: CCI: Charlson Comorbidity Index; CKD: chronic kidney disease; DFU: diabetic foot ulcer; LEA: lower extremity amputation; LEAPP: lower extremity amputation prevention program; SD: standard deviation.

<u>Table 24: Unadjusted 1-year outcomes of LEAPP *versus* non-LEAPP patients.</u>

Unadjusted 1-year outcomes	**LEAPP (*n* = 577)**	**Non-LEAPP (*n* = 2,221)**	***P* value**
Minor LEA	73 (12.7)	244 (11.0)	0.261
Major LEA	31 (5.4)	130 (5.9)	0.659
Death	64 (11.1)	335 (15.1)	**0.015**
Minor LEA/death	131 (22.7)	544 (24.5)	0.371
Major LEA/death	89 (15.4)	436 (19.6)	**0.021**
Mean days from enrollment to minor LEA (SD)	99.0 (107.2)	59.1 (92.8)	**<0.001**
Mean days from enrollment to major LEA (SD)	159.0 (116.7)	84.8 (90.0)	**<0.001**
Mean days from enrollment to death (SD)	201.6 (109.1)	155.9 (112.5)	**0.002**
Mean inpatient admissions (SD)	1.5 (2.0)	1.3 (1.7)	0.052
Mean cumulated LOS, days (SD)	18.1 (35.8)	18.1 (35.3)	0.912
Mean ED visits (SD)	1.6 (2.2)	1.4 (1.9)	0.091
Mean primary care polyclinic visits (SD)	4.1 (4.6)	2.7 (3.5)	**<0.001**
Mean hospital SOC visits (SD)	8.3 (8.3)	4.9 (6.3)	**<0.001**
Mean day surgery procedures (SD)	0.6 (1.7)	0.4 (1.2)	**<0.01**

Abbreviations: ED: emergency department; LEA: lower extremity amputation; LEAPP: lower extremity amputation prevention program; LOS: length of stay; SD: standard deviation; SOC: specialist outpatient clinic.

<u>Table 25: Adjusted 1-year risk of lower extremity amputation and death for LEAPP *versus* non-LEAPP patients.</u>

Adjusted 1-year outcomes	**Odds ratio (OR)**	**P > z**	**95% CI**
Minor LEA	1.15	0.345	0.86, 1.54
Major LEA	0.88	0.560	0.58, 1.34
Death	0.60	**0.001**	0.44, 0.82
Composite of minor LEA/death	0.84	0.128	0.67, 1.05
Composite of major LEA/death	0.66	**0.002**	0.51, 0.86

Note: the non-LEAPP cohort is the reference group—adjusted (logistics regression) for age, gender, ethnicity, diagnosis of diabetic retinopathy, ischemic heart disease (IHD), end-stage renal failure (ESRF), stroke, CKD severity, LEA in the past 1 year, and medications (antiplatelet, anticoagulant, antihypertensive, antidiabetic, and lipid-lowing).

Abbreviations: CI: confidence interval; LEA: lower extremity amputation; LEAPP: lower extremity amputation prevention program.

<u>Table 26: Adjusted 1-year outcomes for LEAPP versus non-LEAPP patients.</u>

Adjusted 1-year outcomes	**LEAPP**	**Non-LEAPP**	**IRR**	***P* value**	**95% CI**
Mean days from enrollment to minor LEA	91.8	60.5	1.52	**<0.001**	1.47, 1.56
Mean days from enrollment to major LEA	145.8	86.9	1.68	**<0.001**	1.62, 1.75
Mean days from enrollment to death	210.7	154.7	1.36	**<0.001**	1.33, 1.39
Mean inpatient admissions (SD)	1.4	1.3	1.09	**0.033**	1.01, 1.18
Mean cumulated LOS, days (SD)	17.4	18.3	0.95	**<0.001**	0.93, 0.97
Mean ED visits (SD)	1.6	1.4	1.10	**0.011**	1.02, 1.19
Mean primary care polyclinic visits (SD)	4.0	2.7	1.48	**<0.001**	1.41, 1.56
Mean hospital SOC visits (SD)	7.8	5.0	1.55	**<0.001**	1.5, 1.61
Mean day surgery procedures (SD)	0.6	0.4	1.52	**<0.001**	1.34, 1.74

Note: The non-LEAPP cohort is the reference group—adjusted (Poisson regression) for age, gender, ethnicity, diagnosis of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, LEA in the past 1 year, and medications (antiplatelet, anticoagulant, antihypertensive, antidiabetic, lipid-lowing).

Abbreviations: CI: confidence interval; ED: emergency department; IRR: incidence rate ratio; LEA: lower extremity amputation; LEAPP: lower extremity amputation prevention program; LOS: length of stay; SD: standard deviation; SOC: specialist outpatient clinic.

Chapter 8: DEFINITE Subgroup Analysis: Characteristics and Outcomes of Patients Who Defaulted on Clinic Follow-ups

Summary

This chapter is the second of four subgroup analyses within DEFINITE Care and analyses clinical outcomes of patients who defaulted on at least one DFU-related clinic appointment at primary or tertiary care between June 2020 and June 2022 (n = 2,798). Overall, there is a high defaulter rate of more than 40% amongst patients with DFU. These patients were generally younger males of Malay or Indian ethnicity and were likely ex-smokers/current smokers. They had fewer comorbidities but worse DM control and poor HbA1c levels. After adjusting for age, gender, ethnicity, comorbidities (IHD, retinopathy, ESRF, and stroke), and medications, patients who defaulted on DFU-related clinic appointments did not have an increased risk of minor LEA, major LEA, or death. However, they exhibited a significant increase in subsequent healthcare utilization for inpatient and outpatient services. In addition, from January 2021 to December 2021 (n = 970), we qualitatively evaluated the reasons for defaulting. Subsequently, we categorized them into modifiable system issues (green), modifiable patient education issues (orange), changes in medical condition (red), and unmodifiable reasons (gray). Approximately two-thirds (64.7%) of the reasons for defaulting were modifiable system issues (37.5%) or patient education issues (27.2%).

Methodology

This part is the second of four subgroup analyses within the DEFINITE Care cohort. The detailed methodology, inclusion and exclusion criteria, overall patient characteristics, and outcomes are discussed in detail in Chapters 5 and 6. This chapter focuses on patients with DFU who defaulted on clinic follow-ups at either primary or tertiary care. At primary care, patients were included as defaulters if they did not attend a scheduled DFU-related clinic appointment with the primary care doctor or the nurse, did not self-schedule and reattend a clinic appointment within 1 week, and did not have a concurrent hospital DFU-related clinic appointment within 1 week. At tertiary care, patients were classified as defaulters if they failed to attend a scheduled DFU-related SOC clinic appointment with a vascular surgeon, orthopedic surgeon, podiatrist, or nurse. Patients who defaulted on primary or tertiary care clinic appointments were highlighted to the Diabetic Foot Coordinators (DFC). DFCs conducted follow-ups with all patients *via* phone calls. Furthermore, from January 2021 to December 2021, we qualitatively evaluated the reasons for defaulting. Subsequently, we categorized them into modifiable system issues (green), modifiable patient education issues (orange), changes in medical condition (red), and unmodifiable reasons (gray) (Figure 19).

Follow-up data on prospective clinical, administrative, and direct healthcare costs were captured within the healthcare cluster's chronic disease management registry for diabetes, with relevant ICD9 and ICD10 diagnosis, surgical procedure, and service codes (Appendix 1). Factors and outcomes were evaluated using descriptive statistics. Percentages were used for categorical data, and means with SDs were used for continuous data. Between-group comparisons for categorical data were made using chi-squared tests, whereas those for continuous data were made using Student's *t*-test. All P values of <0.05 were considered statistically significant, and all P values were two-tailed. ORs of minor LEA, major LEA, and morality were evaluated, using the non-defaulters cohort as the reference group and adjusting (logistical regression) for age, gender, ethnicity, history of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, lipid-lowering medications). IRR between the defaulter and non-defaulter groups for clinical outcomes and healthcare utilization was evaluated using Poisson regression, using the non-defaulters cohort as the reference group and controlling for age, gender, ethnicity, history of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, lipid-lowering medications). All statistical analyses were performed using Microsoft Excel 2016 (Microsoft, Redmond, Washington) and R software version 3.6.1 (R Foundation, Vienna, Austria). This study was approved by the institution's ethics review board (National Healthcare Group Domain Specific Review Board 2021/01154).

Results

Between June 2020 and June 2022, 2,798 patients within the DEFINITE cohort completed a minimum of 12-month follow-up. Of these patients, 1,125 (40.2%) defaulted on at least one clinic appointment at primary or tertiary care, whereas 1,673 (59.8%) did not. The baseline characteristics of both groups are shown in Table 27. Patients in the defaulters cohort were younger, with a mean age of 63.6 *versus* 67.2 years in the non-defaulters cohort ($P < 0.001$). There were significantly more males within the defaulters' cohort (63.7% *vs*. 59.8%, $P = 0.038$), with a higher proportion of patients of Malay (21.1% *vs*. 15.3%) and Indian (22.0% *vs*. 15.5%, $P < 0.001$) ethnicities. There were also more ex-smokers or current smokers (25.7% *vs*. 18.2%, $P < 0.001$). No differences were noted in the history of LEA or CKD status. However, patients in the cohort of defaulters were more likely to have fewer comorbidities with lower CCI (2.5 *vs*. 2.9, $P < 0.001$) but worse DM control with poorer mean HbA1c levels (8.4 *vs*. 7.8, $P < 0.001$) and higher risk of DM retinopathy (40.1% *vs*. 35.5%, $P = 0.013$), despite being on DM medications (86.4% *vs*. 79.7%, $P < 0.001$).

For the unadjusted 1-year outcomes, patients who defaulted on clinic appointments exhibited a significantly higher rate of minor LEA (13.0% *vs*. 10.2%, $P = 0.024$) with a lower rate of death (8.6% *vs*. 18.1%, $P < 0.001$) and resultant lower composite minor LEA/death (20.5% *vs*. 26.5%, $P < 0.001$) and composite major LEA/death (13.5% *vs*. 22.3%, $P < 0.001$) rates (Table 28). Interestingly, despite a higher rate of minor LEA, they had longer mean days from enrollment to minor LEA (84.9 *vs*. 54.1, $P = 0.004$), major LEA (141.5 *vs*. 73.9, $P < 0.001$), and death (205.5 *vs*. 149.7, $P < 0.001$)

Concerning the adjusted 1-year outcomes, using the non-defaulters cohort as the reference group and adjusting (logistical and Poisson regression) for age, gender, ethnicity, diagnosis of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, LEA in the past 1 year, and medications (antiplatelet, anticoagulant, antihypertensive, antidiabetic, and lipid-lowing), there was no increased risk of death (OR 0.50, $P < 0.001$), composite minor LEA/death (OR 0.76, $P = 0.005$), and composite major LEA/death (OR 0.60, $P < 0.001$) among the defaulters (Table 29). In terms of healthcare utilization, the adjusted 1-year outcomes for the defaulters demonstrated a global increase in inpatient and outpatient health service utilization. There was an increase in inpatient admissions (OR 1.20, P < 0.001), ED visits (OR 1.25, P < 0.001), primary care polyclinic visits (OR 1.16, $P < 0.001$), and hospital SOC visits (OR 1.10, $P < 0.001$) (Table 29).

Between January 2021 and December 2021, the DFCs qualitatively evaluated the patients who defaulted on at least one clinic appointment at primary or tertiary care (Figure 19). During the follow-up phone call to the patients who defaulted, patients were asked about the main reasons for defaulting on the scheduled clinic appointment for their DFU care. Of the 970 patients who defaulted during the 12 months, more than one-third (37.5%) indicated modifiable system issues as the main reason for default. The reasons included an overlap of appointments, the caregiver's inability to bring the patient to the appointment, the inability to contact the clinic hotline to reschedule the appointment, or financial difficulties. Furthermore, over one-quarter of patients (27.2%) reported modifiable patient education issues as the main reason for default, including forgetting or being unaware of the scheduled appointment, refusing to attend the clinic despite multiple scheduling efforts, and being busy with other nonmedical appointments. In total, more than one-third of the patients (35.3%) had a change in medical condition or unmodifiable reasons to account for their clinic default. Unfortunately, we did not manage to evaluate the education attainment of the patients for correlation against patient's health activation evaluation or rate of defaulting.

Table 27: Characteristics of defaulters *versus* non-defaulters.

Variables		Defaulters (*n* = 1,125, 40.2%)	Non-defaulters (*n* = 1,673, 59.8%)	*P* value
Age, mean (SD)		63.6 (12.2)	67.2 (12.8)	**<0.001**
Gender				**0.038**
	Male	717 (63.7)	1,001 (59.8)	
	Female	408 (36.3)	672 (40.2)	
Ethnicity				**<0.001**
	Chinese	541 (48.1)	1,019 (60.9)	
	Malay	237 (21.1)	256 (15.3)	
	Indian	247 (22.0)	260 (15.5)	
	Others	100 (8.9)	138 (8.3)	
Smoking status				**<0.001**
	Nonsmoker	456 (40.5)	734 (43.9)	
	Ex-smoker	127 (11.3)	148 (8.9)	
	Current smoker	162 (14.4)	155 (9.3)	
	Unknown	380 (33.8)	636 (38.0)	
History of LEA in the past 1 year		33 (2.9)	40 (2.4)	0.377
Medications				
	Antiplatelet	707 (62.8)	969 (57.9)	**0.009**
	Anticoagulant	186 (16.5)	256 (15.3)	0.381
	Lipid-lowering	916 (81.4)	1,288 (77)	**0.005**
	Antihypertensive	804 (71.5)	1,164 (69.6)	0.283
	DM medications	972 (86.4)	1,333 (79.7)	**<0.001**

HbA1c, mean (SD)	8.4 (2.2)	7.8 (1.9)	**<0.001**
Comorbidities			
CCI, mean (SD)	2.5 (1.5)	2.9 (1.8)	**<0.001**
Hypertension	893 (79.4)	1,342 (80.2)	0.588
Dyslipidemia	919 (81.7)	1,340 (80.1)	0.295
Diabetic retinopathy	451 (40.1)	593 (35.5)	**0.013**
Dementia	46 (4.1)	116 (6.9)	**0.002**
Ischemic heart disease	351 (31.2)	477 (28.5)	0.127
History of stroke	190 (16.9)	297 (17.8)	0.555
End-stage renal failure	190 (16.9)	297 (17.8)	0.555
CKD severity			0.392
No CKD	329 (29.2)	498 (29.8)	
Mild	378 (33.6)	514 (30.7)	
Moderate	245 (21.8)	397 (23.7)	
Severe	173 (15.4)	264 (15.8)	

Abbreviations: CCI: Charlson Comorbidity Index; CKD: chronic kidney disease; DFU: diabetic foot ulcer; LEA: lower extremity amputation; SD: standard deviation.

Table 28: Unadjusted 1-year outcomes of defaulters *versus* non-defaulters.

One-year outcomes	Defaulters (N=1,125)		Non-defaulters (N=1,673)		p-value
	n (%) / mean (SD)	Median (Q1-Q3)	n (%) / mean (SD)	Median (Q1-Q3)	
Binary outcomes					
Minor LEA	146 (13.0)	-	171 (10.2)	-	**0.024**
Major LEA	60 (5.3)	-	101 (6.0)	-	0.433
All-cause mortality	97 (8.6)	-	302 (18.1)	-	**<0.001**
Minor LEA-free survival	231 (20.5)	-	444 (26.5)	-	**<0.001**
Major LEA-free survival	152 (13.5)	-	373 (22.3)	-	**<0.001**
Overall LEA-free survival	266 (23.6)	-	484 (28.9)	-	**0.002**
Healthcare utilisation outcomes					
Number of inpatient admissions	1.5 (2)	1 (0 - 2)	1.2 (1.6)	1 (0 - 2)	**0.001**
Cumulative length of stay	18.1 (31.8)	3 (0 - 19)	18.1 (37.6)	4 (0 - 22)	0.091
Number of DS encounters	0.4 (1.3)	0 (0 - 0)	0.4 (1.3)	0 (0 - 0)	0.079
Number of ED visits	1.7 (2.3)	1 (0 - 2)	1.3 (1.6)	1 (0 - 2)	**<0.001**
Number of SOC visits	3.2 (4.1)	3 (0 - 8)	2.8 (3.7)	4 (0 - 9)	**0.003**
Number of polyclinic visits	6 (7.2)	1 (0 - 5)	5.3 (6.7)	2 (0 - 5)	0.053

Abbreviations: DS: day surgery; ED: emergency department; LEA: lower extremity amputation; LEAPP: lower extremity amputation prevention program; LOS: length of stay; SD: standard deviation; SOC: specialist outpatient clinic.

<u>Table 29: Adjusted 1-year risk of lower extremity amputation and death for defaulters versus non-defaulter patients</u>

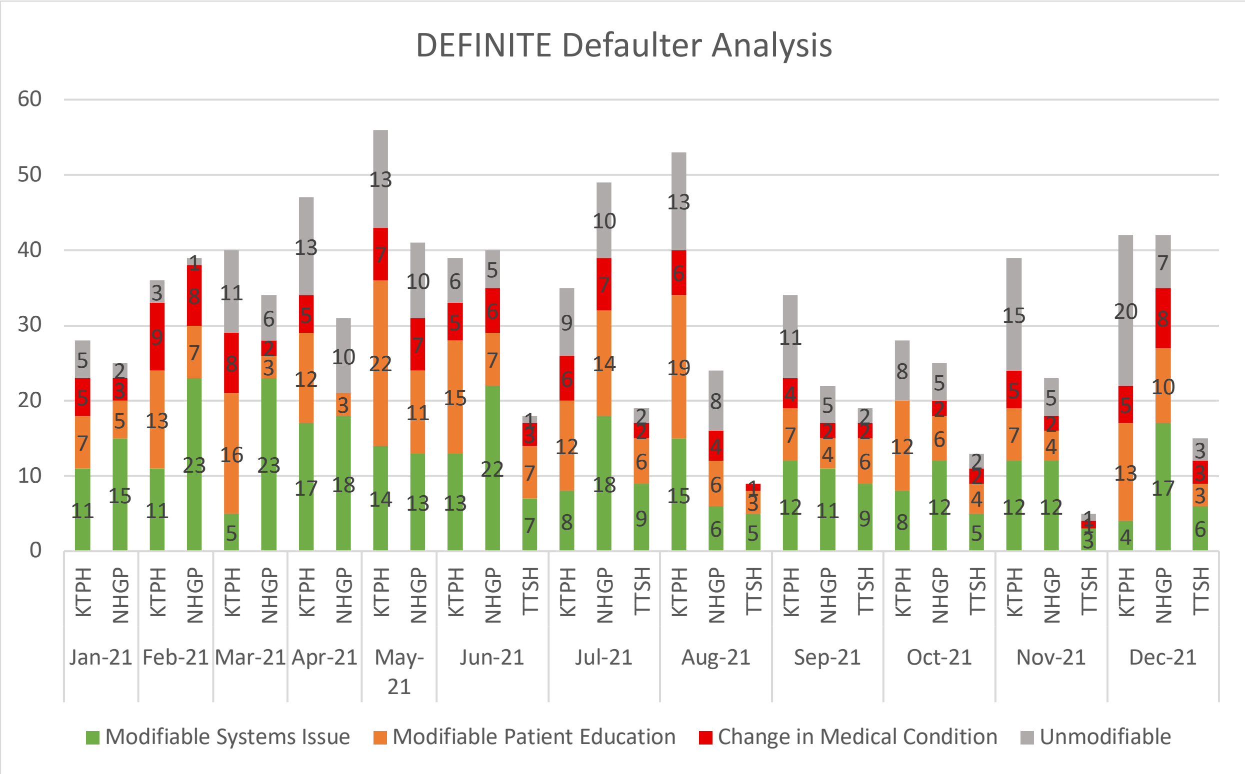
One-year outcomes* (n=2,798)	OR / IRR	95% CI	p-value
Binary outcomes			
Minor LEA	1.18	0.93, 1.51	0.180
Major LEA	0.80	0.56, 1.12	0.193
All-cause mortality	0.50	0.39, 0.65	**<0.001**
Minor LEA-free survival	0.76	0.62, 0.92	**0.005**
Major LEA-free survival	0.60	0.48, 0.75	**<0.001**
Overall LEA-free survival	0.79	0.65, 0.95	**0.012**
Healthcare utilisation outcomes			
Number of inpatient admissions	1.20	1.13, 1.29	**<0.001**
Cumulative length of stay	0.99	0.97, 1.01	0.170
Number of DS encounters	0.89	0.79, 1.00	**0.049**
Number of ED visits	1.25	1.18, 1.34	**<0.001**
Number of SOC visits	1.10	1.05, 1.15	**<0.001**
Number of polyclinic visits	1.16	1.12, 1.20	**<0.001**

* using multiple logistic regression or Poisson regression

Note: the non-defaulters cohort is the reference group—adjusted (logistics regression) for age, gender, ethnicity, diagnosis of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, LEA in the past 1 year, and medications (antiplatelet, anticoagulant, antihypertensive, antidiabetic, and lipid-lowing).

Abbreviations: CI: confidence interval; DS: day surgery; ED: emergency department; IRR: incidence rate ratio; LEA: lower extremity amputation; OR: odds ratio; SOC: specialist outpatient clinic

Figure 19: Number of patients with DFUs who defaulted on clinic appointments, with associated reasons.



	Defaulting reasons (Jan 2021 to Dec 2021)	**Category**	***n* = 970 (%)**
1	Appointment overlap/close to next wound visit	Green: modifiable system issues	364 (37.5%)
2	Caregivers' inability to bring the patient to an appointment		
3	Inability to contact the clinic hotline		
4	Financial difficulties		
5	Forgetting/being unaware of the appointment	Orange: modifiable patient education issues	264 (27.2%)

6	Refusal to attend clinic after multiple scheduling efforts		
7	Patient was busy with other nonmedical appointments		
8	Patient did not feel well	Red: change in medical condition	130 (13.4%)
9	Wound healed/improved		
10	Patient was uncontactable	Gray: unmodifiable reasons	212 (21.9%)
11	Patient preferred care at other institutions		
12	Self-dresses wound		
13	Not willing to share the reason		
14	Others		

(Note: data collection at TTSH only commenced in June 2021)

Abbreviations: DFU: diabetic foot ulcer; KTPH: Khoo Teck Puat Hospital; NHGP: National Healthcare Group Polyclinics; TTSH: Tan Tock Seng Hospital.

Chapter 9: DEFINITE Subgroup Analysis: Characteristics and Outcomes of Octogenarians With DFUs

Summary

This chapter is the third of four subgroup analyses within DEFINITE Care and analyses the clinical outcomes of octogenarians with DFU. This chapter focuses on octogenarians with DFU. It aims to evaluate whether diabetic limb salvage (DLS), associated with multiple procedures and efforts, should be offered to octogenarians, who are often high-risk and frail candidates for surgical procedures with limited life expectancy. Within the control group (2016–2017, *n* = 5,462), octogenarians (*n* = 1,718) constituted 31.5% of the study population. However, within the DEFINITE group (2020–2022, *n* = 2,798), they (*n* = 406) constituted 14.5% of the study population. Overall, a comparison between octogenarians and non-octogenarians revealed a greater percentage of female Chinese non-smokers with better DM control and fewer complications. Expectedly, they had more comorbidities. Despite more aggressive DLS efforts within DEFINITE octogenarians, there were good outcomes of lower major LEA rate, mortality rate, and longer mean days from enrollment to death. Even after adjusting for age, gender, comorbidities, and medications, the benefits of DLS within DEFINITE octogenarians were consistently noted, with a transfer of healthcare utilization from inpatient to outpatient care.

Methodology

This part is the third of four subgroup analyses within the DEFINITE Care cohort. The detailed methodology, inclusion and exclusion criteria, overall patient characteristics, and outcomes are comprehensively investigated in Chapters 5 and 6. This chapter focuses on octogenarians with DFU. Within the control (June 2016–December 2017) and DEFINITE (June 2020–June 2022) cohorts, patients with DFUs aged >80 years were identified. We aim to evaluate whether DLS, involving associated multiple procedures and efforts, should be offered to octogenarians, who are often high-risk candidates for surgical procedures with limited life expectancy.

Follow-up data on prospective clinical, administrative, and direct healthcare costs were captured within the healthcare cluster's chronic disease management registry for diabetes, with relevant ICD9 and ICD10 diagnosis, surgical procedure, and service codes (Appendix 1). Factors and outcomes were evaluated using descriptive statistics. Percentages were used for categorical data, and means with SDs were used for continuous data. Between-group comparisons for categorical data were performed using chi-squared tests, whereas those for continuous data were made using Student's *t*-test. All *P* values <0.05 were considered statistically significant, and all *P* values were two-tailed. ORs of minor LEA, major LEA, and morality were evaluated, using non-octogenarians control group as the reference group and adjusting (logistical regression) for age, gender, ethnicity, history of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, and lipid-lowering medications). IRR between the octogenarians and non-octogenarians for clinical outcomes and healthcare utilization was evaluated using Poisson regression, with the non-octogenarians control group as the reference group and controlling for age, gender, ethnicity, history of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, and lipid-lowering medications). All statistical analyses were performed using Microsoft Excel 2016 (Microsoft, Redmond, Washington) and R software version 3.6.1 (R Foundation, Vienna, Austria). This study was approved by the institution's ethics review board (National Healthcare Group Domain Specific Review Board 2021/01154).

Results

Within the control group (2016–2017, *n* = 5,462), octogenarians (*n* = 1,718) constituted 31.5% of the study population. However, within the DEFINITE group (2020–2022, *n* = 2,798), they (*n* = 406) constituted 14.5% of the study population (Table 30). Overall, a comparison between octogenarians and non-octogenarians revealed a greater percentage of females (59.4%), Chinese (81.0%), and nonsmokers (62.6%) among octogenarians with DFU. Furthermore, octogenarians had better DM control (lower mean HbA1c of 7.1 *vs*. 8.0) than non-octogenarians, but fewer complications (retinopathy 22.6%, ESRF 12.9%, and history of LEA 0.6%), despite having more comorbidities with higher mean CCI at 5.3. When comparing control octogenarians and DEFINITE octogenarians, DEFINITE octogenarians had fewer comorbidities with lower mean CCI (4.6 *vs*. 5.3) and lower percentage of IHD (32.0% *vs*. 40.1%) and ESRF (7.4% *vs*. 14.2%). All were statistically significant with $P < 0.001$.

Concerning the unadjusted 1-year outcomes of control octogenarians *versus* DEFINITE octogenarians (mean age of 86.1 years versus 85.6 years), there was a greater propensity toward DLS within the DEFINITE population, as evident by the higher minor LEA rate (7.1% *vs*. 1.2%, $P = 0.004$) and statistically insignificant shorter mean days from enrollment to minor LEA (50.3 days *vs*. 62.6%, $P = 0.368$) (Table 31). Despite the more aggressive DLS efforts within DEFINITE octogenarians, there were good outcomes of lower major LEA rate (2.2% *vs*. 2.4%, $P = 0.001$), mortality rate (34.7% *vs*. 45.2%, $P < 0.001$), and longer mean days from enrollment to death (152.9 *vs*. 112.3 days, $P = 0.018$), as compared with the control octogenarians. In addition, the DEFINITE octogenarians showed lower inpatient admission episodes (1.4 *vs*. 2.4, $P = 0.041$), shorter LOS (17.3 *vs*. 26.2 days, $P = 0.007$), and a corresponding increase in outpatient care with more primary care polyclinic visits (2.9 *vs*. 1.4, $P < 0.001$) and hospital SOC visits (5.9 *vs*. 2.6, $P < 0.001$).

The benefits of DLS within DEFINITE octogenarians were consistently noted after adjusting (logistical and Poisson regression) for age, gender, ethnicity, diagnosis of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, LEA in the past 1 year, and medications (antiplatelet, anticoagulant, antihypertensive, antidiabetic, and lipid-lowing), using the non-octogenarians control group as the reference group. Although there was a higher OR for minor LEA among DEFINITE octogenarians (1.49 *vs*. 0.25, $P < 0.001$), there was consistently lower OR for major LEA (0.51 *vs*. 0.57, $P = 0.002$) and death (1.87 *vs*. 2.44, $P < 0.001$) compared with the control octogenarians (Table 32). There was a transfer of healthcare utilization from inpatient to outpatient care. For DEFINITE octogenarians, the IRR for inpatient admissions was 0.61 *versus* 0.99 ($P < 0.001$), and that for the mean cumulated LOS was 0.75 *versus* 1.04 ($P < 0.001$). Additionally, the IRR for mean primary care polyclinic visits was 1.46 *versus* 0.77 ($P < 0.001$), and that for hospital SOC visits was 1.97 *versus* 0.89 ($P < 0.001$) (Table 33).

Table 30: Characteristics of octogenarians *versus* non-octogenarians for the control and DEFINITE groups.

Variables		Control group (2016–2017) (*n* = 5,462)			DEFINITE group (2020–2022) (*n* = 2,798)		
		Octogenarians (*n* = 1,718, 31.5%)	**Non-octogenarians (*n* = 3,744, 68.5%)**	***P* value**	**Octogenarians (*n* = 406, 14.5%)**	**Non-octogenarians (*n* = 2,392, 85.5%)**	***P* value**
Age, mean (SD)		86.1 (4.7)	64.9 (10.2)	**<0.001**	85.6 (4.7)	62.4 (10.3)	**<0.001**
Gender				**<0.001**			**<0.001**
	Male	691 (40.2)	2,245 (60.0)		172 (42.4)	1,546 (64.6)	
	Female	1,027 (59.8)	1,499 (40.0)		234 (57.6)	846 (35.4)	
Ethnicity				**<0.001**			**<0.001**
	Chinese	1,392 (81.0)	2,191 (58.5)		328 (80.8)	1,232 (51.5)	
	Malay	126 (7.3)	642 (17.2)		20 (4.9)	473 (19.8)	
	Indian	126 (7.3)	607 (16.2)		42 (10.3)	465 (19.4)	
Smoking status				**<0.001**			**<0.001**
	Nonsmoker	1,126 (65.5)	2,113 (56.4)		203 (50.0)	987 (41.3)	
	Ex-smoker	137 (8.0)	518 (13.8)		27 (6.7)	248 (10.4)	
	Current smoker	65 (3.8)	517 (13.8)		11 (2.7)	306 (12.8)	
	Unknown	390 (22.7)	596 (15.9)		165 (40.6)	851 (35.6)	
History of LEA in the past 1 year		9 (0.5)	77 (2.1)	**<0.001**	4 (1.0)	69 (2.9)	**0.026**

Medications						
Antiplatelet	1,025 (59.7)	2,205 (58.9)	0.592	266 (65.5)	1,410 (59.0)	**0.012**
Anticoagulant	252 (14.7)	717 (19.2)	**<0.001**	66 (16.3)	376 (15.7)	0.784
Lipid-lowering	1,237 (72.0)	3,074 (82.1)	**<0.001**	316 (77.8)	1,888 (78.9)	0.617
Antihypertensive	1,366 (79.5)	3,180 (84.9)	**<0.001**	289 (71.2)	1,679 (70.2)	0.686
DM	1,037 (60.4)	3,061 (81.8)	**<0.001**	283 (69.7)	2,022 (84.5)	**<0.001**
HbA1c, mean (SD)	7.1 (1.6)	8.0 (2.3)	**<0.001**	7.2 (1.5)	8.2 (2.1)	**<0.001**
Comorbidities						
CCI, mean (SD)	5.3 (1.8)	3.3 (1.9)	**<0.001**	4.6 (1.8)	2.5 (1.4)	**<0.001**
Hypertension	1,671 (97.3)	3,517 (93.9)	**<0.001**	365 (89.9)	1,870 (78.2)	**<0.001**
Dyslipidemia	1,600 (93.1)	3,477 (92.9)	0.724	347 (85.5)	1,912 (79.9)	**0.009**
Diabetic retinopathy	398 (23.2)	1,389 (37.1)	**<0.001**	83 (20.4)	961 (40.2)	**<0.001**
Dementia	840 (48.9)	480 (12.8)	**<0.001**	90 (22.2)	72 (3.0)	**<0.001**
Ischemic heart disease	689 (40.1)	1,477 (39.5)	0.646	130 (32.0)	698 (29.2)	0.247
History of stroke	794 (46.2)	1,264 (33.8)	**<0.001**	100 (24.6)	387 (16.2)	**<0.001**
End-stage renal failure	244 (14.2)	873 (23.3)	**<0.001**	30 (7.4)	449 (18.8)	**<0.001**
CKD severity			**<0.001**			**<0.001**
No CKD	210 (12.2)	783 (20.9)		81 (20.0)	746 (31.2)	
Mild	352 (20.5)	1,125 (30.1)		72 (17.7)	820 (34.3)	
Moderate	684 (39.8)	1011 (27.0)		170 (41.9)	472 (19.7)	
Severe	472 (27.5)	825 (22.0)		83 (20.4)	354 (14.8)	

Abbreviations: CCI: Charlson Comorbidity Index; CKD: chronic kidney disease; DFU: diabetic foot ulcer; LEA: lower extremity amputation; LEAPP: lower extremity amputation prevention program; SD: standard deviation.

Table 31: Unadjusted 1-year outcomes of octogenarians *versus* nonoctogenarians for the control and DEFINITE groups.

Unadjusted 1-year outcomes	**Control group (2016–2017) (*n* = 5,462)**			**DEFINITE group (2020–2022) (*n* = 2,798)**		
	Octogenarians (*n* = 1,718, 31.5%)	**Non-octogenarians (*n* = 3,744, 68.5%)**	***P* value**	**Octogenarians (*n* = 406, 14.5%)**	**Non-octogenarians (*n* = 2,392, 85.5%)**	***P* value**
Minor LEA	20 (1.2)	239 (6.4)	**<0.001**	29 (7.1)	288 (12.0)	**0.004**
Major LEA	42 (2.4)	217 (5.8)	**<0.001**	9 (2.2)	152 (6.4)	**0.001**
Death	777 (45.2)	898 (24.0)	**<0.001**	141 (34.7)	258 (10.8)	**<0.001**
Minor LEA/death	790 (46.0)	1,108 (29.6)	**<0.001**	160 (39.4)	515 (21.5)	**<0.001**
Major LEA/death	809 (47.1)	1,055 (28.2)	**<0.001**	146 (36.0)	379 (15.8)	**<0.001**
Mean days from enrollment to minor LEA (SD)	62.55 (93.44)	56.17 (90.41)	0.368	50.28 (68.51)	70.08 (99.94)	0.886
Mean days from enrollment to major LEA (SD)	81.86 (69.6)	82.76 (89.78)	0.347	135.11 (134.35)	96.95 (97.42)	0.552

Mean days from enrollment to death (SD)	112.33 (111.25)	124.07 (111.98)	**0.018**	152.89 (116.05)	168.92 (111.29)	0.114
Mean inpatient admissions (SD)	2.38 (1.81)	2.53 (2.07)	0.144	1.39 (1.59)	1.32 (1.81)	**0.041**
Mean cumulated LOS, days (SD)	26.17 (28.24)	26.38 (33.17)	**<0.001**	17.32 (27.78)	18.21 (36.54)	**0.007**
Mean ED visits (SD)	2.47 (2.05)	2.74 (3.12)	**0.036**	1.49 (1.65)	1.45 (1.98)	0.074
Mean primary care polyclinic visits (SD)	1.44 (2.83)	1.99 (3.13)	**<0.001**	2.86 (3.87)	3 (3.82)	0.318
Mean hospital SOC visits (SD)	2.56 (4.21)	2.94 (5.28)	0.217	5.85 (7.21)	5.55 (6.85)	0.817
Mean day surgery procedures (SD)	0.10 (0.47)	0.26 (0.86)	**<0.001**	0.17 (0.71)	0.45 (1.37)	**<0.001**

Abbreviations: ED: emergency department; LEA: lower extremity amputation; LEAPP: lower extremity amputation prevention program; LOS: length of stay; SD: standard deviation; SOC: specialist outpatient clinic.

<u>Table 32: Adjusted 1-year risk of lower extremity amputation and death of octogenarians *versus* non-octogenarians for the control and DEFINITE groups.</u>

Adjusted 1-year outcomes	**Odds ratio (OR)**	**P > z**	**95% CI**
Minor LEA			
Control octogenarians	0.25	**<0.001**	0.16, 0.40
Control non-octogenarians	1	-	-
DEFINITE octogenarians	1.49	0.061	0.98, 2.25
DEFINITE non-octogenarians	1.84	**<0.001**	1.52, 2.22
Major LEA			
Control octogenarians	0.57	**0.002**	0.40, 0.81
Control non-octogenarians	1	-	-
DEFINITE octogenarians	0.51	0.058	0.26, 1.02
DEFINITE non-octogenarians	1.07	0.566	0.85, 1.34
Death			
Control octogenarians	2.44	**<0.001**	2.13, 2.80
Control non-octogenarians	1	-	-
DEFINITE octogenarians	1.87	**<0.001**	1.48, 2.35
DEFINITE non-octogenarians	0.44	**<0.001**	0.37, 0.51
Composite of minor LEA/death			
Control octogenarians	2.08	**<0.001**	1.83, 2.38
Control non-octogenarians	1	-	-
DEFINITE octogenarians	1.80	**<0.001**	1.44, 2.25
DEFINITE non-octogenarians	0.73	**<0.001**	0.64, 0.82
Composite of major LEA/death			
Control octogenarians	2.27	**<0.001**	1.78, 2.31
Control non-octogenarians	1	-	-
DEFINITE octogenarians	1.66	**<0.001**	1.34, 2.08
DEFINITE non-octogenarians	0.53	**<0.001**	0.66, 0.84

Note: the non-octogenarians control group is the reference group—adjusted (logistics regression) for age, gender, ethnicity, diagnosis of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, LEA in the past 1 year, and medications (antiplatelet, anticoagulant, antihypertensive, antidiabetic, and lipid-lowing).

Abbreviations: CI: confidence interval; LEA: lower extremity amputation.

<u>Table 33: Adjusted 1-year outcomes of octogenarians *versus* non-octogenarians for the control and DEFINITE groups.</u>

Adjusted 1-year outcomes	**Value**	**IRR**	***P* value**	**95% CI**
Mean inpatient admissions (SD)				
Control octogenarians	2.41	0.99	0.658	0.94, 1.04
Control non-octogenarians	2.43	1	-	-
DEFINITE octogenarians	1.49	0.61	**<0.001**	0.55, 0.69
DEFINITE non-octogenarians	1.37	0.56	**<0.001**	0.53, 0.60
Mean cumulated LOS, days (SD)				
Control octogenarians	26.28	1.04	0.260	0.97, 1.12
Control non-octogenarians	25.22	1	-	-
DEFINITE octogenarians	18.90	0.75	**<0.001**	0.64, 0.88
DEFINITE non-octogenarians	19.27	0.76	**<0.001**	0.70, 0.84
Mean ED visits (SD)				
Control octogenarians	2.53	0.96	0.144	0.90, 1.02
Control non-octogenarians	2.65	1	-	-
DEFINITE octogenarians	1.62	0.61	**<0.001**	0.54, 0.69
DEFINITE non-octogenarians	1.49	0.56	**<0.001**	0.53, 0.60
Mean primary care polyclinic				
visits (SD)	1.52	0.77	**<0.001**	0.69, 0.86
Control octogenarians	1.97	1	-	-
Control non-octogenarians	2.87	1.46	**<0.001**	1.27, 1.68
DEFINITE octogenarians	2.95	1.50	**<0.001**	1.39, 1.62
DEFINITE non-octogenarians				
Mean hospital SOC visits (SD)				
Control octogenarians	2.55	0.89	**0.020**	0.80, 0.98
Control non-octogenarians	2.88	1	-	-
DEFINITE octogenarians	5.66	1.97	**<0.001**	1.73, 2.25
DEFINITE non-octogenarians	5.80	2.02	**<0.001**	1.87, 2.18
Mean day surgery procedures (SD)				
Control octogenarians	0.13	0.51	**<0.001**	0.39, 0.66

Control non-octogenarians	0.25	1	-	-
DEFINITE octogenarians	0.21	0.84	0.422	0.55, 1.29
DEFINITE non-octogenarians	0.40	1.59	**<0.001**	1.35, 1.87

Note: the non-octogenarians control group is the reference group—adjusted (Poisson regression) for age, gender, ethnicity, diagnosis of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, LEA in the past 1 year, and medications (antiplatelet, anticoagulant, antihypertensive, antidiabetic, lipid-lowing)

Abbreviations: CI: confidence interval; ED: emergency department; IRR: incidence rate ratio; LEA: lower extremity amputation; LOS: length of stay; SD: standard deviation; SOC: specialist outpatient clinic.

Chapter 10: DEFINITE Subgroup Analysis: Characteristics and Outcomes According to Primary Care Catchment Population

Summary

This chapter is the final subgroup analysis within DEFINITE Care and analyses characteristics and outcomes according to the primary care catchment population. Our public healthcare cluster serves a multi-ethnic (Chinese, Malay, and Indian) and elderly (17% over 65 years) population catchment of 2.2 million in central and northern Singapore, with an integrated network of seven primary care polyclinics (2.4 million combined yearly attendances). Primarily, patients in the north were served by the WDL and YIS polyclinics, whereas patients in the central catchment were served by the AMK, TP, HOU, GEY, and KAL polyclinics. Significantly, almost half the population within DEFINITE had primary care doctors from outside of our healthcare cluster or were followed up by private general practitioners. Compared to patients with primary care needs provided outside of our healthcare cluster, patients followed up with NHGP had significantly higher amputation-free survival. Although the youngest patients were from the northern catchment, it had the highest proportion of Malay and Indian ethnicities, with the highest proportion of active smokers, the highest level of mean HbA1c, and a high prevalence of ESRF. Consequently, patients from the north had the highest rates of minor and major LEAs, the shortest mean days from enrollment to minor and major LEAs, and the highest mean inpatient admissions.

Methodology

This part is the final subgroup analysis within the DEFINITE Care cohort. The detailed methodology, inclusion and exclusion criteria, overall patient characteristics, and outcomes are investigated in detail in Chapters 5 and 6. This chapter discusses the characteristics and outcomes of patients with DFUs according to the primary care catchment population. Our public healthcare cluster serves a multiethnic (Chinese, Malay, and Indian) and elderly (17% over 65 years) population catchment of 2.2 million in central and northern Singapore, with an integrated network of seven primary care polyclinics (2.4 million combined yearly attendances) [42]. Figure 20 shows the location of all seven polyclinics (WDL, YIS, AMK, TP, HOU, GEY, and KAL) with their catchment population. Primarily, patients in the north (green and blue) were served by the WDL and YIS polyclinics. Patients in the central catchment (orange and purple) were served by the AMK, TP, HOU, GEY, and KAL polyclinics. The numbers for the GEY and KAL polyclinics were combined owing to the close proximity, small numbers, and KAL being a new site (established for approximately 12 months). Significantly, almost half the population within DEFINITE had primary care doctors from outside the NHG polyclinics (there are two other public healthcare clusters in Singapore) or were followed up by private general practitioners, which did not have a common EMR system with the public healthcare cluster.

Follow-up data on prospective clinical, administrative, and direct healthcare costs were captured within the healthcare cluster's chronic disease management registry for diabetes, with relevant ICD9 and ICD10 diagnosis, surgical procedure, and service codes (Appendix 1). Factors and outcomes were evaluated using descriptive statistics. Percentages were used for categorical data, and means with SDs were used for continuous data. Between-group comparisons for categorical data were performed using chi-squared tests, whereas those for continuous data were made using Student's *t*-test. All *P* values of <0.05 were considered statistically significant, and all *P* values were two-tailed. ORs of minor LEA, major LEA, and morality were evaluated, using non-NHGP patients as the reference group and adjusting (logistical regression) for age, gender, ethnicity, history of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, and lipid-lowering medications). IRR between NHGP patients and non-NHGP patients for clinical outcomes and healthcare utilization was evaluated using Poisson regression, using non-NHGP patients as the reference group and controlling for age, gender, ethnicity, history of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, lower extremity amputation history in the past 1 year, and medications (antiplatelet, anticoagulation, antihypertensives, DM medications, and lipid-lowering medications). All statistical analyses were performed using Microsoft Excel 2016 (Microsoft, Redmond, Washington) and R software version 3.6.1 (R Foundation, Vienna, Austria). This study was approved by the institution's ethics review board (National Healthcare Group Domain Specific Review Board 2021/01154).

Results

Within DEFINITE Care (June 2020–June 2022, *n* = 2,798), approximately half the patients (*n* = 1,406, 50.3%) had their primary care needs followed up within the public healthcare cluster's network of seven polyclinics (Figure 20). The youngest patients were from the northern catchment of WDL (61.5 years) and YIS (63.4 years), whereas the oldest patients were from the central catchment of TPY (67.6 years) and AMK (67.6 years) (Table 34). The highest proportion of males were from the central catchment of TPY (66.2%) and GEY/KAL (76.8%). The northern catchment of WDL and YIS had the highest proportion of Malay ethnicity (28.2% and 19.8%, respectively) and Indian ethnicity (24.1% and 23.2%, respectively). However, the central catchment of TPY, AMK, and GEY/KAL showed the highest proportion of Chinese ethnicity (62.8%, 67.3%, and 64.6%, respectively). In addition, patients from the northern catchment of WDL and YIS had the highest proportion of active smokers (14.9% and 16.4%, respectively). Those from the central catchment of TPY and AMK demonstrated the highest risk of LEA in the past 1 year (18.0% and 16.6%, respectively). Patients from the northern catchment of WDL and YIS showed the highest mean HbA1c levels (8.0 and 8.6, respectively), in which the value for patients from TPY was high at 8.3. Similar to the age profile, patients from the northern catchment of WDL and YIS demonstrated the lowest mean CCI (2.3 and 2.5, respectively), whereas patients from the central catchment of TPY and GEY/KAL had the highest mean CCI (2.8 for both). The ESRF prevalence was the highest among the northern catch of WDL and YIS (11.7% and 15.7%, respectively), with GEY/KAL high at 14.5%.

When evaluating the unadjusted 1-year outcomes of patients with DFUs across the landscape, the rate of minor LEA was highest within the northern catchment of WDL and YIS (13.9% and 17.4%, respectively), with the highest rates of major LEA within the northern catchment of WDL and YIS (5.4% and 5.5%, respectively) (Table 35). This result is associated with the shortest mean days from enrollment to minor LEA (63.8 days for WDL and 76.3 days for YIS) and the shortest mean days from enrollment to major LEA (161.4 days for WDL and 84.1 days for YIS). Correspondingly, patients from the northern catchment demonstrated the highest mean inpatient admissions (1.2 for WDL and 1.5 for YIS), with a high mean LOS (12.5 days for WDL and 15.0 days for YIS). Similar to the comorbidity profile, patients from the central catchment of TPY and AMK showed the highest mean LOS (16.4 and 15.6 days, respectively), mean polyclinic visits (5.6 and 5.3, respectively), and mean hospital SOC visits (6.5 and 6.0, respectively).

After adjusting (logistics and Poisson regression) for age, gender, ethnicity, diagnosis of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, LEA in the past 1 year, and medications (antiplatelet, anticoagulant, antihypertensive, antidiabetic, and lipid-lowing) and using non-NHGP patients as the reference group, patients followed up with NHGP (within the healthcare cluster) had significantly higher amputation-free survival. There was a global lower OR among NHGP for major amputation (OR of 0.22–0.82) and mortality (OR of 0.26–0.75), as compared to patients with primary care needs managed outside of our healthcare cluster. In addition, patients on active follow-up with NHGP demonstrated consistently lower mean cumulated LOS (IRR of 0.45–0.90) and more primary care polyclinic visits (IRR of 3.70–4.82) (Table 36). When comparing geographical outcomes within NHGP sites, there is a consistent trend of patients from the north with the highest OR for minor LEA (1.51 for WDL and 1.87 for YIS) and major LEA (0.82 for WDL and 0.76 for YIS) (Table 37), which corresponds to poorer DM control with more DM complications, as described earlier.

It must be noted that due to their locations, patients from the HOU and GEY polyclinics may have hospital SOC visits at a hospital outside our public health cluster, whereas the KAL polyclinic had only been in operation for 12 months, hence skewing results.

Table 34: Characteristics of patients with DFUs across various polyclinic catchments.

Variables		Non-NHGP (*n* = 1,392, 49.8%)	WDL (*n* = 316, 11.3%)	YIS (*n* = 293, 10.5%)	TPY (*n* = 250, 8.9%)	HOU (*n* = 248, 8.9%)	AMK (*n* = 217, 7.8%)	GEY/KAL (*n* = 82, 2.9%)	*P* value
Age, mean (SD)		66.7 (13.1)	61.5 (11.4)	63.4 (11.7)	67.6 (12.2)	64.7 (11.9)	67.6 (12.8)	66.9 (13.2)	**<0.001**
Gender									**<0.001**
	Male	802 (57.6)	209 (66.1)	194 (66.2)	177 (70.8)	143 (57.7)	130 (59.9)	63 (76.8)	
	Female	590 (42.4)	107 (33.9)	99 (33.8)	73 (29.2)	105 (42.3)	87 (40.1)	19 (23.2)	
Ethnicity									**<0.001**
	Chinese	815 (58.6)	100 (31.7)	142 (48.5)	157 (62.8)	147 (59.3)	146 (67.3)	53 (64.6)	
	Malay	254 (18.3)	89 (28.2)	58 (19.8)	17 (6.8)	44 (17.7)	19 (8.8)	12 (14.6)	
	Indian	207 (14.9)	76 (24.1)	68 (23.2)	57 (22.8)	44 (17.7)	42 (19.4)	13 (15.9)	
Smoking status									**<0.001**
	Nonsmoker	460 (33.1)	172 (54.4)	140 (47.8)	148 (59.2)	138 (55.7)	122 (56.2)	10 (12.2)	
	Ex-smoker	108 (7.8)	43 (13.6)	49 (16.7)	24 (9.6)	35 (14.1)	16 (7.4)	0 (0)	
	Current smoker	128 (9.2)	47 (14.9)	48 (16.4)	28 (11.2)	25 (10.1)	32 (14.8)	9 (11.0)	
	Unknown	696 (50)	54 (17.1)	56 (19.1)	50 (20.0)	50 (20.2)	47 (21.7)	63 (76.8)	
History of LEA in the past 1 year		275 (19.8)	45 (14.2)	43 (14.7)	45 (18.0)	35 (14.1)	36 (16.6)	8 (9.8)	**0.025**

Medications								
Antiplatelet	935 (67.2)	160 (50.6)	179 (61.1)	144 (57.6)	111 (44.8)	115 (53.0)	32 (39.0)	**<0.001**
Anticoagulant	282 (20.3)	41 (13.0)	48 (16.4)	22 (8.8)	12 (4.8)	30 (13.8)	7 (8.5)	**<0.001**
Lipid-lowering	1,141 (82.0)	242 (76.6)	231 (78.8)	207 (82.8)	180 (72.6)	165 (76.0)	38 (46.3)	**<0.001**
Antihypertensive	1,038 (74.6)	218 (69.0)	212 (72.4)	183 (73.2)	143 (57.7)	145 (66.8)	29 (35.4)	**<0.001**
DM	1,148 (82.5)	270 (85.4)	262 (89.4)	208 (83.2)	199 (80.2)	176 (81.1)	42 (51.2)	**<0.001**
HbA1c, mean (SD)	8.0 (2.1)	8.6 (2.3)	8.3 (2.1)	7.9 (1.9)	7.9 (1.9)	7.7 (1.6)	8.0 (1.8)	**<0.001**
Comorbidities								
CCI, mean (SD)	2.9 (1.8)	2.3 (1.3)	2.5 (1.7)	2.8 (1.6)	2.5 (1.4)	2.8 (1.6)	3.4 (2)	**<0.001**
Hypertension	1,137 (81.7)	246 (77.9)	233 (79.5)	202 (80.8)	191 (77)	178 (82)	48 (58.5)	**<0.001**
Dyslipidemia	1,123 (80.7)	258 (81.7)	235 (80.2)	208 (83.2)	208 (83.9)	183 (84.3)	44 (53.7)	**<0.001**
Diabetic retinopathy	584 (42.0)	90 (28.5)	119 (40.6)	71 (28.4)	71 (28.6)	87 (40.1)	22 (26.8)	**<0.001**
Dementia	123 (8.8)	5 (1.6)	4 (1.4)	12 (4.8)	4 (1.6)	14 (6.5)	0 (0)	**<0.001**
Ischemic heart disease	425 (30.5)	93 (29.4)	96 (32.8)	70 (28)	63 (25.4)	64 (29.5)	17 (20.7)	0.278
History of stroke	275 (19.8)	45 (14.2)	43 (14.7)	45 (18)	35 (14.1)	36 (16.6)	8 (9.8)	**0.025**
End-stage renal failure	313 (22.5)	37 (11.7)	46 (15.7)	28 (11.2)	22 (8.9)	21 (9.7)	12 (14.6)	**<0.001**
CKD severity								**<0.001**
No CKD	358 (25.7)	99 (31.3)	90 (30.7)	82 (32.8)	93 (37.5)	56 (25.8)	49 (59.8)	
Mild	420 (30.2)	114 (36.1)	104 (35.5)	69 (27.6)	88 (35.5)	80 (36.9)	17 (20.7)	
Moderate	332 (23.9)	74 (23.4)	66 (22.5)	63 (25.2)	43 (17.3)	55 (25.4)	9 (11.0)	
Severe	282 (20.3)	29 (9.2)	33 (11.3)	36 (14.4)	24 (9.7)	26 (12.0)	7 (8.5)	

Abbreviations: CCI: Charlson Comorbidity Index; CKD: chronic kidney disease; DFU: diabetic foot ulcer; LEA: lower extremity amputation; SD: standard deviation.

Table 35: Unadjusted 1-year outcomes of patients with DFUs across various polyclinic catchment

Unadjusted 1-year outcomes	**Non-NHGP (*n* = 1,392, 49.8%)**	**WDL (*n* = 316, 11.3%)**	**YIS (*n* = 293, 10.5%)**	**TPY (*n* = 250, 8.9%)**	**HOU (*n* = 248, 8.9%)**	**AMK (*n* = 217, 7.8%)**	**GEY/KAL (*n* = 82, 2.9%)**	***P* value**
Minor LEA	145 (10.4)	44 (13.9)	51 (17.4)	31 (12.4)	10 (4.0)	24 (11.1)	12 (14.6)	**<0.001**
Major LEA	107 (7.7)	17 (5.4)	16 (5.5)	8 (3.2)	4 (1.6)	8 (3.7)	1 (1.2)	**<0.001**
Death	286 (20.6)	15 (4.8)	28 (9.6)	15 (6)	23 (9.3)	21 (9.7)	11 (13.4)	**<0.001**
Minor LEA/death	399 (28.7)	59 (18.7)	73 (24.9)	45 (18)	32 (12.9)	45 (20.7)	22 (26.8)	**<0.001**
Major LEA/death	363 (26.1)	31 (9.8)	41 (14)	23 (9.2)	27 (10.9)	28 (12.9)	12 (14.6)	**<0.001**
Mean days from enrollment to minor LEA (SD)	55.2 (93.7)	63.8 (73.7)	76.3 (106.9)	98.2 (111.2)	79.1 (95.1)	85 .0 (104.3)	88.7 (123.1)	0.076
Mean days from enrollment to major LEA (SD)	78.8 (94.8)	161.4 (89.7)	84.1 (68.5)	133.3 (123.6)	182.5 (119.1)	167.1 (91.4)	304 (90.0)	**<0.001**
Mean days from enrollment to death (SD)	152.3 (114.1)	192.7 (110.5)	166.4 (105.6)	211.4 (110.8)	202.6 (91.3)	205.4 (110.5)	172 (122.9)	**0.024**
Mean inpatient admissions (SD)	1.5 (1.8)	1.2 (1.9)	1.5 (1.6)	1.3 (1.8)	0.5 (0.9)	1.5 (2.1)	1.3 (1.8)	**<0.001**

Mean cumulated LOS, days (SD)	22.9 (41.7)	12.5 (24)	15.0 (23.8)	16.4 (32.3)	7.1 (25.2)	15.6 (29.8)	13.9 (26.4)	**<0.001**
Mean ED visits (SD)	1.5 (1.9)	1.6 (2.2)	1.7 (1.7)	1.4 (1.8)	0.6 (1.4)	1.7 (2.5)	1.3 (1.8)	**<0.001**
Mean primary care polyclinic visits (SD)	1.1 (2.2)	5.1 (3.8)	4.3 (3.6)	5.6 (3.9)	5.6 (4.7)	5.3 (4.7)	0.2 (0.7)	**<0.001**
Mean hospital SOC visits (SD)	6.1 (6.8)	4.3 (5.4)	5.8 (6.2)	6.5 (7.5)	3.1 (6.5)	6.0 (9)	4.9 (7.4)	**<0.001**
Mean day surgery procedures (SD)	0.4 (1.1)	0.4 (1.3)	0.4 (1.4)	0.4 (1.4)	0.4 (1.8)	0.5 (1.4)	0.3 (0.8)	0.730

Abbreviations: ED: emergency department; LEA: lower extremity amputation; LEAPP: lower extremity amputation prevention program; LOS: length of stay; SD: standard deviation; SOC: specialist outpatient clinic.

Table 36: Adjusted 1-year risk of lower extremity amputation and death of patients with DFUs across various polyclinic catchments.

Adjusted 1-year outcomes	**Odds ratio (OR)**	**P > z**	**95% CI**
Minor LEA			
WDL	1.51	**0.038**	1.02, 2.21
YIS	1.87	**0.001**	1.30, 2.68
TPY	1.44	0.096	0.94, 2.22
HOU	0.47	**0.025**	0.24, 0.91
AMK	1.36	0.204	0.85, 2.19
GEY/KAL	2.22	**0.022**	1.12, 4.38
Major LEA			
WDL	0.82	0.477	0.47, 1.43
YIS	0.76	0.347	0.44, 1.34
TPY	0.53	0.094	0.25, 1.11
HOU	0.30	**0.020**	0.11, 0.82
AMK	0.64	0.249	0.30, 1.36
GEY/KAL	0.22	0.138	0.03, 1.63
Death			
WDL	0.31	**<0.001**	0.18, 0.54
YIS	0.53	**0.005**	0.34, 0.83
TPY	0.26	**<0.001**	0.15, 0.45
HOU	0.62	0.055	0.38, 1.01
AMK	0.43	**0.001**	0.26, 0.71
GEY/KAL	0.75	0.428	0.37, 1.52
Composite of minor LEA/death			
WDL	1.79	0.154	0.57, 1.09
YIS	1.00	0.986	0.74, 1.36
TPY	0.63	**0.011**	0.44, 0.90
HOU	0.54	**0.003**	0.36, 0.81
AMK	0.79	0.201	0.54, 1.14
GEY/KAL	1.24	0.435	0.72, 2.12

Composite of major LEA/death			
WDL	0.46	**<0.001**	0.30, 0.63
YIS	0.57	**0.003**	0.39, 0.82
TPY	0.32	**<0.001**	0.20, 0.51
HOU	0.53	**0.005**	0.34, 0.83
AMK	0.48	**0.001**	0.31, 0.75
GEY/KAL	0.63	0.175	0.33, 1.23

Note: non-NHGP patients constitute the reference group—adjusted (logistics regression) for age, gender, ethnicity, diagnosis of diabetic retinopathy, IHD, ESRF, stroke, severity of CKD, LEA in the past q year, and medications (antiplatelet, anticoagulant, antihypertensive, antidiabetic, and lipid-lowing).

Abbreviations: CI: confidence interval; LEA: lower extremity amputation; NHGP: national healthcare group polyclinics.

<u>Table 37: Adjusted 1-year outcomes of patients with DFUs across various polyclinic catchments.</u>

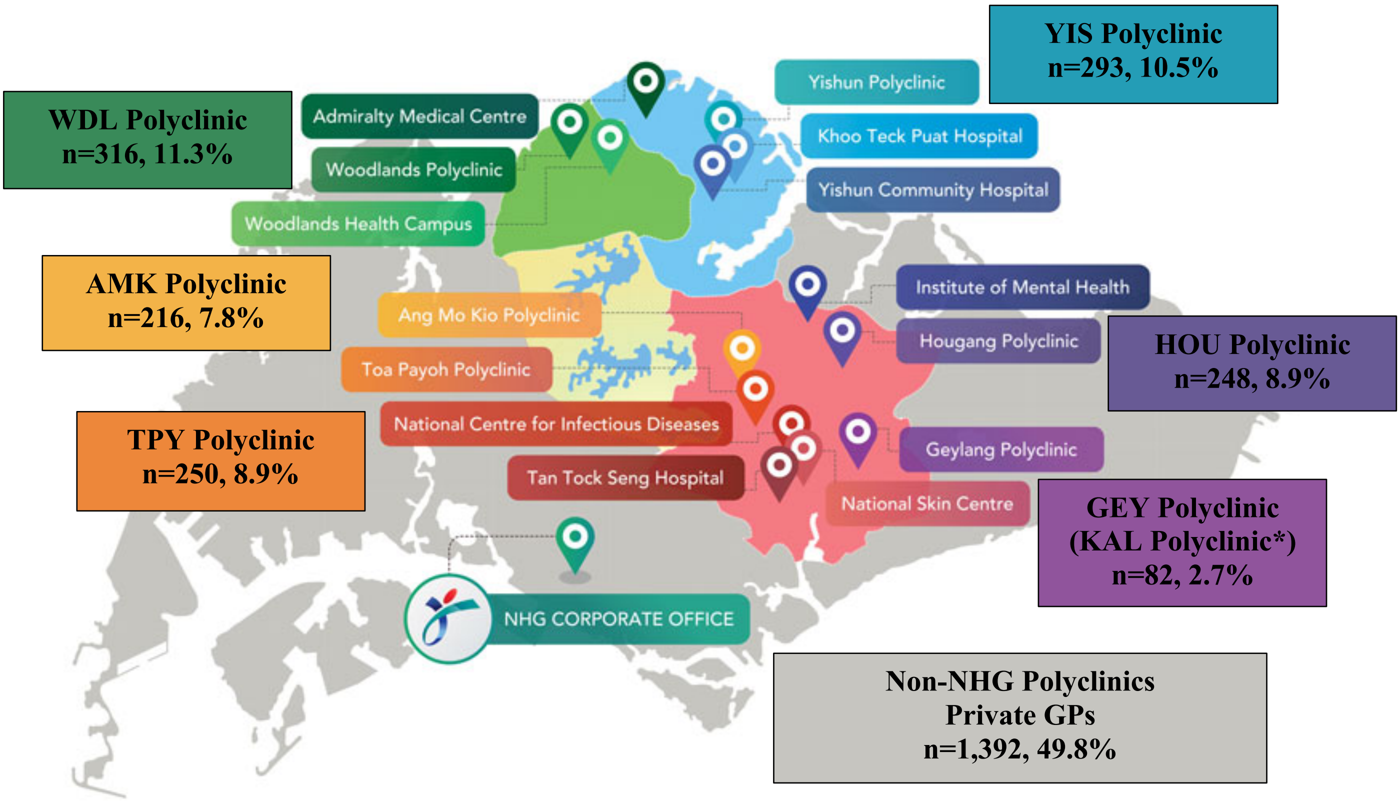
Adjusted 1-year outcomes	**IRR**	***P* value**	**95% CI**
Mean inpatient admissions (SD)			
WDL	0.98	0.702	0.87, 1.10
YIS	1.08	0.147	0.97, 1.20
TPY	1.05	0.397	0.94, 1.18
HOU	0.42	**<0.001**	0.35, 0.51
AMK	1.15	**0.025**	1.02, 1.29
GEY/KAL	1.26	**0.023**	1.03, 1.54
Mean cumulated LOS, days (SD)			
WDL	0.68	**<0.001**	0.66, 0.71
YIS	0.73	**<0.001**	0.71, 0.76
TPY	0.86	**<0.001**	0.83, 0.89
HOU	0.45	**<0.001**	0.43, 0.47
AMK	0.83	**<0.001**	0.80, 0.86
GEY/KAL	0.90	**<0.001**	0.84, 0.95
Mean ED visits (SD)			
WDL	1.15	**0.005**	1.04, 1.28
YIS	1.14	**0.008**	1.04, 1.27
TPY	1.03	0.613	0.92, 1.16
HOU	0.50	**<0.001**	0.42, 0.59
AMK	1.23	**<0.001**	1.10, 1.37
GEY/KAL	1.13	0.218	0.93, 1.39
Mean primary care polyclinic visits (SD)			
WDL	4.37	**<0.001**	4.07, 4.70
YIS	3.70	**<0.001**	3.43, 3.99
TPY	4.68	**<0.001**	4.35, 5.04
HOU	4.82	**<0.001**	4.48, 5.20
AMK	4.43	**<0.001**	4.10, 4.78
GEY/KAL	0.18	**<0.001**	0.11, 0.30

Mean hospital SOC visits (SD)			
WDL	0.87	**<0.001**	0.82, 0.93
YIS	1.04	0.166	0.98, 1.09
TPY	1.11	**<0.001**	1.05, 1.17
HOU	0.62	**<0.001**	0.58, 0.67
AMK	1.03	0.373	0.97, 1.09
GEY/KAL	1.17	**0.002**	1.06, 1.30
Mean day surgery procedures (SD)			
WDL	1.07	0.474	0.88, 1.31
YIS	1.01	0.881	0.84, 1.23
TPY	1.09	0.429	0.88, 1.37
HOU	1.32	**0.008**	1.07, 1.63
AMK	1.26	**0.030**	1.02, 1.56
GEY/KAL	1.02	0.909	0.68, 1.55

Note: non-NHGP patients constitute the reference group—adjusted (Poisson regression) for age, gender, ethnicity, diagnosis of diabetic retinopathy, IHD, ESRF, stroke, CKD severity, LEA in the past 1 year, and medications (antiplatelet, anticoagulant, antihypertensive, antidiabetic, and lipid-lowing)

Abbreviations: CI: confidence interval; ED: emergency department; IRR: incidence rate ratio; LEA: lower extremity amputation; LOS: length of stay; NHGP: national healthcare group polyclinics; SD: standard deviation; SOC: specialist outpatient clinic.

Figure 20: Distribution of DEFINITE Care patients across seven primary care polyclinics (2020–2022, *n* = 2,798).



* Note: numbers for GEY and KAL polyclinics were combined owing to the close proximity, small numbers, and KAL being a new site.

Chapter 11: Digital Health: A Qualitative Study on Patients, Carers, and Healthcare Providers' Perspectives on a Patient-Owned Surveillance System for DFU Care

Summary

Digital health has recently gained a foothold in monitoring and improving diabetes care. DEFINITE Care aims to utilize wound imaging technology in DFU wound monitoring. We aim to explore the views of patients, carers, and healthcare providers (HCPs) in relation to the use of a novel patient-owned wound surveillance application as part of outpatient management of patients with DFUs. The qualitative study encompassed 20 patients, five carers, and 20 HCPs. Regarding a patient-owned wound surveillance application, patients, carers and HCPs were all open and receptive to the system, and workflow for use in DFU care. Four major themes emerged from patients and carers: (1) technology, (2) application features and usability, (3) feasibility of using the wound imaging application, and (4) logistics of care. Four major themes were identified from HCPs: (1) attitudes toward wound imaging application, (2) preferences regarding functionality, (3) perceived challenges for patients/carers, and (4) perceived barriers for HCPs. These findings demonstrate the potential of digital health and areas to improve and tailor a DFU wound application suitable for implementation in the local population. Results from subsequent pilot clinical study will be presented in Chapter 12.

Methodology

Semi-structured interviews were conducted *via* video teleconferencing between June and October 2021. Interviews were conversational, and items were not asked verbatim or in the order presented in the interview guide (Appendices 3, 4, and 5). Purposive maximum variation sampling was used to select participants with varying attributes, such as ethnicity, education, employment, and whether they had previously used their phones to take photos of their foot wounds. This offered a better representation of the Singapore population and ensured heterogeneity to capture common themes related to the wound imaging application. Participants were recruited from a primary polyclinic network and two tertiary hospitals in Singapore. Ethics approval was obtained from the local institutional ethics board (National Healthcare Group DSRB reference: 2020/01347).

<u>Study participants</u>

There were three categories of participants: patients with diabetes, carers of patients with diabetes, and HCPs. The inclusion criteria for patients were as follows: age of 21 years or above, community-dwelling, ability to speak English or Mandarin, self-reported diabetes, and being affected by DFU for more than 3 months. Patients with severe mental illness who lacked the capacity for self-care and participants with severe communication difficulties were excluded. The inclusion criteria for carers were as follows: not professionally qualified (family member, friends, and domestic helpers), aged 21 years or older, capable of communicating English or Mandarin (both are commonly used languages in Singapore), and directly involved in the day-to-day care of community-dwelling patients with DFUs for at least 3 months. HCPs comprised various representatives from the multidisciplinary management of DFUs, including surgeons, primary care physicians, nurses, podiatrists, and diabetologists from a primary care polyclinic network and two tertiary hospitals in Singapore.

Data collection

After obtaining informed consent, patients and carers were required to complete a brief sociodemographic survey. For patients and carers, an individual interview was arranged. For HCPs, the interviews were conducted through focus group discussion, comprising four HCPs per group. Participants were notified that the interview was audio recorded. The participants were also shown a 1-min orientation video of the InSight application (eKare Inc., Virginia, USA) as an example of a wound imaging application.

According to the International Organization for Standardization (ISO) 9241-210:2019 definition of human-centered design, our approach to systems design and development aimed "to make interactive systems more usable by focusing on the use of the system and applying human factors/ergonomics and usability knowledge and techniques" [56]. Therefore, these qualitative semi-structured interviews were conducted using flexible, prompt guides to facilitate discussions. Regarding the interviews with HCPs, they were asked about their demographics (years of experience in wound care and job title) and proposed implementation of wound application, perceptions of challenges for adoption, factors that will facilitate adoption, and preferences for features of the application for wound management (Appendix 5). During interviews with patients (Appendix 6) and carers (Appendix 7), open-ended questions were posed on topics such as their current usage of mobile applications, their views on the application, and any improvements that might motivate them to use the application.

In each interview, a designated notetaker was responsible for observing and providing a high-level description of the interview proceedings, including participant feedback and any critical moments in the discussion. A post-interview memo was written after each interview session as a reflection by the notetaker. Interview notes and post-interview memos were employed as references during data analysis.

Data analysis

To increase the trustworthiness of this study, we implemented several strategies to improve credibility, transferability, and confirmability. First, we transcribed the audio recordings in full verbatim and included time stamps. The audio recordings for the interviews conducted in Mandarin were transcribed in their original language and then translated into English. This approach ensured data accuracy and improved the transferability of the study by providing a clear methodology for data analysis. Second, we conducted a thematic analysis to identify common themes, which enabled us to divide the large amount of data from the in-depth interviews into meaningful categories. An initial coding scheme was generated based on key thoughts from the participants. Subsequently, the codes were sorted based on their relationships. Team members reviewed the transcripts multiple times to thoroughly understand the interviews and extract their deeper meanings. This approach improved the confirmability of this study by demonstrating a systematic and transparent approach to data analysis. Finally, emergent categories from the data were grouped into meaningful clusters, representing the major themes and subthemes of this study. These strategies increased the trustworthiness of this study and provided reliable and valid results.

Results

Patients and carers

This study included 20 patients and five carers. The mean age of patients was 61 ± 9, whereas the carers were younger, with a mean age of 45 ± 17. All carers and 90% of the patients had at least a primary school education. Approximately 45% of patients and 40% of carers were employed at the time of the interviews. Half of the patients used their phones to take pictures of their foot wounds. The patient and carer demographics are outlined in Table 38.

Patients and carers participating in this study were open and positive to the concept of a patient-owned wound imaging system for DFU care. Participants expressed their perspectives on personal experiences and preferences in relation to application usage. From the participants' views and experiences (RQ1), four key themes were identified: (1) technology, (2) application features and usability, (3) feasibility of using the wound imaging application, and (4) logistics of care. Table 39 summarizes the key themes along with their subthemes and specific examples.

Technology

Technology is a major theme identified in this study. It determines the acceptability of introducing a new application to patients and carers. In addition, a common subtheme of internet and smartphone accessibility emerged. Contrary to the prevailing belief that the elderly lack technological proficiency, most participants had internet access and used smartphone applications in their daily routines for various needs, including online shopping and communication with family and friends. Social media plays a significant role in the daily routines of patients and carers because most patients use their smartphones for interaction purposes. For example, different social media platforms were discussed, such as Facebook, YouTube, Messenger, Instagram, Twitter, WeChat, and Zoom:

“*Facebook, I have mine, my wife will see what the news is in Singapore,*”

“*I have like this Zoom app, I have a lot of crazy app, Twitter. I have my Signal, I have my Telegram, I have my WeChat, I have my WhatsApp*.”

A few participants considered their smartphones useful for health purposes, mainly for scheduling medical appointments:

“and then the HealthHub, normally I go for my appointments on this, yeah”

However, some participants felt reluctant to use an application because of their limited technological literacy skills:

“Because why I’m, I’m not very, very good using the phone.”

Application features and usability

Another theme that emerged from participants’ experiences and preferences is application features and usability. The components of this theme are the ease of use and preferred features. Participants reported that the ease of use was vital. One of the participants felt very positive about using the wound imaging application. However, she expressed the necessity of simplifying it for older users, such as step-by-step prompts on which buttons to click to execute specific functions:

"I'm actually quite impressed with the apps that I,..., about the wound care-thing. Uh, uh, I think it is, it's the simpler it is, the better it is because, like I said, most, most diabetic people with wounds are normally above 50 and above, most of the time."

Most participants recommended features that would be useful in the application. One notably preferred feature addresses the need for more information on foot care through the images shared with their HCPs. Patients receive information from different specialties, which can be confusing if not effectively consolidated. Therefore, another preferred feature is a readily accessible repository of patient education information, such as the source and cause of the wounds and diets to be adopted to avoid further deterioration of the infection.

"More information. Because it takes a long time for the wound to heal. Everybody wants to know how fast can you heal the wound and what other things can help. Which other things... I, I look forward to."

Furthermore, participants preferred more language options within the application to cater to users whose primary language is not English. In Singapore, it is not uncommon for patients with DFUs to hire foreign domestic helpers as carers. In these cases, English is usually not their first language, and more language options would be beneficial. Therefore, it is significant to investigate the provision of language options for carers because some patients with DFUs, especially those with physical disabilities, rely on their carers to help them take photos of their wounds.

<u>Feasibility of using the wound imaging application</u>

The theme of application feasibility was investigated during the participants' discussions. This theme was further crystallized into subthemes, such as acquiring the habit of taking wound images, acceptance and nonacceptance of application usage, challenges in taking photos of the wounds, and assurance about the benefits and usage of the application. Most participants were not accustomed to the practice of taking photos of their wounds. This task was normally performed by a podiatrist at the clinic or hospital during the visit.

"So far it's all taken by the, the, the podiatrist, yeah."

"Only the, the doctors and the nurses do the taking of the photo."

Having the patients/carer learn the intricacies of wound imaging may be a barrier in the initial stages. Reducing the learning curve would help participants learn and develop the habit of taking photos of their wounds. Nevertheless, when asked about their willingness to acquire proficiency in utilizing the application, most participants expressed acceptance and interest in using a wound imaging application to monitor and manage their wound condition. Most patients agreed to follow the doctor's instructions on taking photographs of their wound using an application:

"*If I'm being told so, by my doctor or the specialist told me to do that, I think I would follow through… my personal, ah, conclusion is that I, would use the experts like doctors you know. Because they would be the best people to tell me how to manage."*

Another subtheme uncovered by this study was the challenges in using the wound imaging application to capture images. To take photos of their foot wounds, they would need to get into an ideal position and be able to visualize the wound relatively clearly. Most patients with visual impairment or other physical disabilities experienced challenges in taking photos of the wound especially because the wound was on the sole of the foot. Because of these challenges, most patients revealed that they required support from family members, carers, or HCPs. One participant explained that nurses and his children were primarily engaged in cleaning and dressing the wound:

> "M*y children, uh, my siblings, um, even the nurses, uh, those take care of me, ... before the wound nurse we engage, before that, my daughter is the one who do the cleaning for me and dressing up the wound."*

> and owing to their age,
>
> "*but very old people, those old-timers, maybe they have problem. Maybe their kids must help*"

This view was also upheld by one of the carers of a patient with DFU:

> *"Uh, I think uh, it's very difficult for her to take photos herself because she lost her, uh, right eyesight. […] So she cannot see very clearly. And then, uh, it's very hard for her to take a picture on her own."*

This shows that it might be quite difficult for patients, especially the elderly or those with more disabilities, to take photos of their wounds and might require help from a caretaker for clear and accurate photos.

Some patients mentioned that they would be more inclined to use the application if they understood how it could benefit them.

"I, I wouldn't know [unclear] because I just take a picture and then I just compare. I don't know how is that going to help me, help me, I don't understand."

"How, how are you going to help us by taking photo? What other benefits I, I get and so on?"

Other patients required assurance regarding the correct utilization of the application before fully committing. This hesitancy might stem from the fear that they would jeopardize the clinical information provided to HCPs, leading to poor management of their DFUs.

"If I learn how to, if I know how to use it, yes, I will do it"

<u>Logistics of care</u>

The logistics of care was another theme discussed by the participants. The first subtheme in the logistics of care is time-saving and flexibility. Patients believed that such an application might allow them to save time normally spent scheduling appointments or visiting clinics for dressings. During the COVID-19 pandemic, it may offer flexibility through remote monitoring by sharing wound photographs with HCPs without necessitating clinic visits:

"*Even sometimes, like, for, for this pandemic, if I have to stay home, I don't go, so that at least I can still check on my wound more regularly."*

However, some patients exhibited a preference for in-person consultation and indicated willingness to use the application if there was no other way to see a doctor:

> *"but it will be much more better if you yourself go there and, uh, let the doctor look at it and take photos. I think it will… It, it really will help to see what really is lah… This [remote consultation] is the second, second option lah. If you cannot go then, you can use the Zoom lah or take photos lah."*

An interesting finding is that younger patients valued the convenience of a wound imaging application, whereas older patients preferred in-person interactions with their HCPs.

Healthcare providers

This study enrolled 20 HCPs: 6 primary care practitioners and 14 tertiary care practitioners (five surgeons, three primary care doctors, five nurses, five podiatrists, and two diabetologists) (Table 40).

Four major themes were identified for three research questions: (1) attitudes toward wound imaging application for RQ2, (2) preferences for functionality for RQ3, (3) perceived challenges for patients/carers, and (4) perceived barriers for HCPs for RQ4. Table 41 shows a summary of the key themes along with their subthemes and specific examples.

Attitudes toward wound imaging application:

The attitudes toward wound imaging applications were discussed and further broken down into attitudes regarding the sharing of information among HCPs, quality of wound assessment and documentation, remote monitoring and early detection, and the use of the application in promoting patient compliance. All HCPs were generally supportive of the wound imaging application.

HCPs agreed that wound images enable effective information sharing across various disciplines (e.g., medical, nursing, and podiatry). Additionally, they facilitate smooth information sharing across institutions from primary to tertiary care. This unfettered information sharing is essential because patients with DFUs often alternate between primary and tertiary institutions for their wound care dressings and reviews. Currently, no wound imaging system is securely shared within the healthcare cluster's EMRs, which will greatly enhance wound assessment and documentation.

> *"I actually… I think that having patient owning the app actually transcends all boundaries of IT barriers, so they can be from SingHealth cluster, NUH cluster. GPs who doesn't own anything, they can all view the, the wound progression together with the patient."*

Some HCPs felt that objective measurement would support seamless and smooth documentation across various HCPs in different institutions, giving HCPs greater confidence in wound management. This would be vital in standardizing wound care documentation because HCPs have different training and calibers.

> *"And it helps with our documentation, right, then I think that will help to save time. And if it synchronizes well with the current electronic medical record system that we are using, then I think that, that would be very beneficial. And I think the AI, probably, has more standardized way, as compared to different clinicians […]"*

"I, I think the, the big advantage is the fact that the wounds are serially documented. In a public healthcare setting, the doctor seeing it may not always be the same person who saw who saw previously. So, it is good to have the reference point, so yeah."

However, there was some skepticism regarding the validity of artificial intelligence:

"we must be reassured of the validity of the AI because I think there's quite a few systems out there, and some of them claim that they are able to classify the various structures. But if, if they even… If they say they could, uh, how do I know that they really could identify the structures correctly."

HCPs felt that the regular and remote monitoring of DFU due to its convenience would enable early detection of wound deterioration. Additionally, it would help save time for patients and reduce hospital waiting times.

"Ah, actually a lot of the diabetic foot, it will be adequately managed at home if they are young, ah, and with the technology. They're able to take accurate picture and send for reference or for some care advice. That'll be great, because you find that they're all working, and they got no time to actually come to hospital, and each time when they come to hospital, they have to wait a long time."

"Yes, because there are times where the patients cannot come for wound reviews or they have difficulty coming. Such apps would help us, as the other… The other people have mentioned, so early detection, uh, of any complications for the wounds."

Furthermore, most HCPs agreed that proactive wound monitoring would help improve health literacy and promote patient compliance with wound care management because it encouraged patients to take greater ownership of their condition:

> *"Actually, we empower the younger patient, and actually with this available, the photograph, to able to contact the healthcare ASAP. […] So, it would be good, so it would be good to actually have this system, to actually empower the patient to take care of themselves and have the healthcare system to actually support them at home."*

Preferences regarding functionality

HCPs possessed diverse preferences concerning the functionality and features of the application, including in-app prompts, the AI's ability to identify wound characteristics and compare them with previous wounds, additional information for patients, and adjustable application settings in terms of changing the language or increasing font size. These preferences were mainly related to improving the user experience for the patient and the quality of medical information obtained from the wound image while not overloading the patient or the healthcare system.

Furthermore, HCPs suggested building in-app prompts to remind patients/carers about wound care or wound imaging schedules. Additionally, some HCPs felt that an SOS "return advice" might be useful for the patient:

> *"You know they may forget about using it, I don't know if anyone would be there to like, give them reminders, I think that might be helpful."*

> *"I'm just thinking whether SOS kind of information would be useful, what do you look out for if you do see this, this, this, please approach your doctor, or something. Ya, so at least they know when to escalate, in terms of the deterioration of the wounds. […] Mm, I think if it's used correctly, then I think it would be useful."*

Conversely, there were concerns that the SOS prompts may cause an additional burden on the healthcare system if not implemented properly or unnecessarily triggered:

> *"It would place unnecessary stress. on the other hand, whoever is receiving the SOS."*
> *"So, if... I mean, really, if there's a case for this SOS button, it's good to, maybe, have some questions prior to that, lah. Like are you experiencing any [unclear] or increasing discharges, and so on, before you press SOS button."*

HCPs also felt that visual representations and identification of wound characteristics would inform patients/carers of their wound progress. Given that the wound was not visualized and examined in person by the HCP, having the prompt and the ability to upload multiple images would allow a more accurate assessment of the wound instead of just a single picture and view:

> *"Yeah I think sometimes when the, ah, especially if it's only one wound image, um, you don't really get an accurate representation of what the wound may be like. […] So, I don't know if like, you could add more pictures to it, like one of it, one of the wound, one of the foot, and then one of the front of the foot, then you may be able to understand a bit more about."*

Additionally, HCPs opined that it would be beneficial for the application to help record wound details. Suggestions were made for the application to have push notifications upon receipt of wound updates to HCPs, email reports, dashboard, and utilization of AI algorithms to highlight deteriorating wounds, such as an increase in size, worsening wound characteristics, or any reported symptoms, such as pain, fever, smell, redness, or discharge:

> *"I think the app itself, right, can, can help in recording the wound details, like the wound description, for example, how many percent granulation, how many percent slough, and identify bone."*

Additionally, some HCPs wanted a functionality allowing them to compare the wounds with previous images to trend patients' recovery:

> *"But in terms of progress, will there be a graph to show, you know, the, the wound size coming down?"*

> *"It will be good if the only measures can be set by the previous wound and the latest wound then you can at least visually compare. Then if the details of the wound can be also side by side, that'll be very useful."*

Regarding accessibility, HCPs were mainly concerned about whether patients and carers could use the application with reference to language and text size. They suggested the addition of more languages, the option to enlarge font size, and the inclusion of audio instructions:

"Because I think the ability to adjust the font size and choose the language, right, in the mother tongue, so it would be quite important."

"Um, but I think the problem is that those people with retinopathy, they probably can't see very well. Like, the words or the instructions to follow, so maybe if you have, like, audio… Like, you know, an audio aspect to it, it might help lah."

In terms of additional features outside wound imaging, most HCPs felt that the main aim of the application would revolve around enabling patients to independently document their wound images.

Furthermore, some HCPs proposed incorporating the diabetic and wound care plan into the application, along with providing bite-sized information, to help patients manage their diabetes and wounds. They felt that the provision of diabetic and wound care plans would help educate patients/carers and improve health literacy:

"I think some basic education would be good, but it's more that I think it shouldn't be a new knowledge kind of thing. It should be for reinforcement because I suppose this group of patient would have seen a healthcare professional before embarking on this app, right? So it should be, like, basic diabetes… Uh, basic wound care… Wound care advice that they just need to follow. […] Um, I think diabetic care plan, it's, uh… It's good to have a brief overview for, for them lah so that they know how, um… You know, that all, all… Like, this… All these matters lah, you know, your blood sugar control."

"I think simple, bite-sized information like what dressing to use, when to change when it's soaked."

Conversely, some believed in the significance of achieving a balance to prevent overwhelming the patient. They emphasized that the application should focus on the main goal of wound imaging, and not include too many details:

"Because if it's too overwhelming, sometimes, they would just decide not to receive any. Ya. So, for diabetic care plan, I mean, maybe not necessary for patient with wounds going on because it might be too much for them."

"I just want to see wound image. What dressing is being put on, and what is the plan for the wound. Because it is a wound app, need to focus the wound app."

<u>Perceived challenges for patients/carers</u>

Most HCPs were concerned with potential perceived challenges for patients/carers. These ranged from physical challenges resulting from patients' physical disabilities to mindset challenges driven by patients' hesitance or noncompliance in utilizing the wound imaging application.

In terms of user suitability, application adoption will require a select group of patients and carers who are willing, possess smartphone/internet access, and can be adequately trained. HCPs felt this application might not be feasible for patients with visual impairments or other comorbidities that may result in poor-quality photographs.

"Um, yeah, for the patients that I'm seeing, I think they would find it quite challenging, because they've got mobility issues, they can't bend, the eyesight is very poor as well, don't know if they've got that kind of support."

Others also mentioned that the application would only be feasible for more stable patients and not those with more serious wounds, which may result in adverse outcomes, such as amputation.

"The patients… The patients who are suitable are those with very stable wounds. They come every one to two months just to ensure… Just for us to ensure that the wound is recovered. Wounds can partially be managed either by podiatrist or by the polyclinic nurses, so these are the subset of patients that are suitable. Those that are not suitable are those whereby the wounds are questionable and those who are pending amputation but patient is, like, deciding."

In terms of acceptability, most HCPs felt that patients would appreciate the convenience of managing their wounds at home:

"I definitely feels that, uh, our patients will see a role in having wound app in… Using wound app in future because we… For, for, for our team, we already have patient taking photo and send it, WhatsApp to us, and ask us for opinion on how to manage the wound […] This is the trend, and it actually minimize patient from coming back to hospital, so nowadays, patients are… They are very independent. They wanted to do their own self-care at home […]"

However, they anticipated possible resistance from elderly patients who might be averse to technology:

"And, and, also, on the receiving end for elderly, I'm not sure how receptive they are with regards to the tech itself. Because quite, quite a lot of elderlies, you know, they are still quite lacking in the tech idea."

This might pose a significant problem because a significant proportion of the patient group was elderly:

"So, for the patient wise, I would say majority of our patient groups here, I mean, for diabetic, or our supervision, they are pretty old and, and lack of caregiver sometimes. So, I think the accepting level should be quite low in our polyclinic."

Noncompliance was another important challenge that could hinder the effectiveness of the application. Most HCPs agreed that the application might suit individuals who are more compliant and technology savvy:

"So, those people who are quite engaged in, you know, their wound health status, probably would be useful. And of course, people who are tech savvy [...]"

However, some shared their concern that compliance with application utilization could be challenging because this wound application requires the person to cultivate the habit of taking wound images. Therefore, they agreed that the application would not be suitable for individuals who had poor compliance or were generally more nonchalant about their condition:

"However, there are a small subset of patients who have very poor compliance, very poor social support, and I would not recommend this for."

Perceived barriers for HCPs

HCPs felt that several barriers could limit the effectiveness of the wound imaging application, including integration with the existing healthcare system, cost to the quality of the wound image, and risks of worsening patient outcomes if wound deterioration was missed.

Application compatibility with the existing EMR system was a major concern. All HCPs expressed apprehensions that more time would be needed to navigate the complex process of integrating the application into the hospital's EMRs:

"compatible or not with your system is another concern. So… And personally, I feel, also, whether it is really time-consuming, and all this thing is another issue for us because due to the patient load and everything."

"Time consumption is definitely an issue because from my understanding of previous platforms, because it's not that compatible, we actually have double work that we actually do some data entry into the app."

Concerning diagnostic accuracy, HCPs felt that the wound image quality, accuracy of wound description, measurements, and additional wound-related questionnaires, such as pain, fever, smell, redness, and discharge, would be pertinent. Some HCPs were concerned about the effect of camera quality, angle, or lighting on wound image quality and, consequently, the overall accuracy of the analysis:

"I feel that the person taking the, ah, ah, quality of the camera, how easy for the, how easy for the, the patient is the potential family member, can he actually reach and, and take a good shot of the wound. And also, ah, family member lighting may not be optimum and that can translate to poorer picture and affect the analysis."

Another HCP reported that the wound image might not be an accurate representation without prior cleaning and debridement, which was occasionally performed during in-person visits by the patient:

"Uh, we need to be quite careful with that because I think, especially with diabetic foot ulcer, sometimes it's very… It's not very clear where the wound is, and sometimes without all the cleaning and debridement, you know, taking a photo of it doesn't tell you much at all what's going on underneath."

Finally, queries were raised about the cost of the wound imaging system to the healthcare system and the patients:

"Then I will also think that costs, whether there will be any cost impact. So, whether it's through organization or through patients. Now, whether this additional cost of the tool will be transferred to the patients as well."

"*and secondly, also, the maintenance of the system, whether or not it will take a lot of cost to maintain."*

Table 38: Sociodemographic characteristics of patients and carers.

Characteristics		Patient (*n* = 20)	Carer (*n* = 5)
Age, mean (SD)		60.9 (9.45)	44.8 (17.09)
Sex, *n* (%)			
	Male	15 (75.0)	1 (20.0)
	Female	5 (25.0)	4 (80.0)
Ethnicity, *n* (%)			
	Chinese	13 (65.0)	1 (20.0)
	Malay	2 (10.0)	2 (40.0)
	Indian	5 (25.0)	1 (20.0)
Education level, *n* (%)			
	No formal education	2 (10.0)	0
	Primary	3 (15.0)	1 (20.0)
	Secondary	7 (35.0)	3 (60.0)
	Tertiary	8 (40.0)	1 (20.0)
Employed, *n* (%)		9 (45.0)	2 (40.0)
Previously used personal phone to take pictures of foot wounds? *n* (%)		10 (50.0)	1 (20.0)

*Categorical variables are presented as *n* (%), and continuous variables are presented as mean (standard deviation).

Table 39: Themes with specific examples from patients and carers.

Theme	Subtheme	Specific examples for each theme
Technology	Internet and smartphone accessibility	• Most patients had internet access and were already using smartphone applications, such as WhatsApp or Facebook, on a daily basis for communication and interaction with friends.
	Health and technology literacy	• Some patients were reluctant to use the application because of their lack of technological literacy skills.
Application features and usability	Ease of use	• Participants expressed the importance of a user-friendly application, especially for older users, a larger proportion of patients with DFUs.
	Preferred features	• Some patients requested features that would transform the application into a resource where they could access information about foot care, such as how to avoid further deterioration of the infection. • Others suggested that more language options would be useful for users whose first language is not English. This would also include those with foreign domestic helpers who help to care for patients with DFUs.
Feasibility of using the wound imaging application	Habit of taking wound image	• Most participants did not have the habit of taking their own pictures. Most of the pictures were taken by the podiatrist in the clinic or hospital during the visit.
	Acceptance	• Most participants expressed acceptance and interest in using a wound imaging application that would help them monitor and care for their wound conditions.

		• Most patients agreed to follow the doctor's instructions on taking photos of their wounds using the application.
	Challenges in taking wound photos	• Many patients experienced difficulty taking photos of the wound owing to visual impairments or physical disabilities. • Many of these patients received support from their families in terms of cleaning and dressing their wounds.
Logistics of care	Time saving and flexibility	• They also felt this flexibility was useful for remote monitoring, especially during the COVID-19 pandemic, allowing them to share wound images with their HCPs without going to the clinic. • Moving forward, patients believed the application would help them save time normally spent making appointments or traveling to clinics.
	Preference for in-person consultations	• Some patients would still prefer in-person consultations because they feel they would receive better care if their HCP could examine the wound in person.

Table 40: Characteristics of healthcare providers (HCPs)

Characteristics	Healthcare providers (*n* = 20)
Level of care	
Primary care	6 (30)
Tertiary care	14 (70)
Profession	
Surgeons	5 (25)
Primary care doctors	3 (15)
Nurses	5 (25)
Podiatrists	5 (25)
Diabetologists	2 (10)

*Categorical variables are presented as *n* (%).

Table 41: Themes with specific examples from healthcare providers (HCPs)

Themes	Subthemes	Specific examples from each theme
Attitudes toward wound imaging application	Enable information sharing among HCPs	• Patients could share their wound progression with any medical professional without the problem of this information being stuck in a specific healthcare institution.
	Wound assessment and documentation	• The software algorithm might be able to standardize wound documentation compared to various healthcare providers. • However, some skepticism arose regarding the validity of artificial intelligence.
	Remote monitoring and early detection	• Convenience of monitoring using the application could aid in early detection and improve outcomes. • Convenience of remote monitoring could help save time for patients and reduce waiting times in the hospital.
	Promote patients' compliance	• Improved patient education would enable individuals to take greater ownership of their conditions.
Preferences regarding functionality	Prompts	• HCPs suggested in-built prompts to remind patients and carers about scheduled wound care or wound surveillance timing. • Some HCPs felt that an SOS "return advice" might benefit the patient. • However, some also felt it might burden the healthcare system if not implemented properly and easily triggered.

	Visual representations and identification of wound characteristics	• HCPs felt it would be beneficial for the application to help record wound details. • Some HCPs requested the function of comparing with the previous wound and a possible graph to show wound progression. • Other HCPs hoped that patients and carers could upload multiple images to accurately represent the wound despite being unable to see it in person.
	Accessibility features	• HCPs were mainly concerned about whether patients and carers could use the application in terms of language and text size. They suggested adding more languages, enlarging the font size, and providing audio instructions.
	General information, diabetic and wound care plan	• Most HCPs felt that the main aim of the application would be for the patient to document their own wound images. • Some HCPs suggested that it might be good for the application to incorporate the diabetic and wound care plan or provide some bite-sized information to help patients manage their diabetes and wounds. However, others felt this might be overwhelming for the patient.
Perceived challenges for patients/carers	Suitability of user	• HCPs felt this application might not be suitable for patients with visual impairments or other comorbidities that make it difficult to take good-quality photos. • Others mentioned that the application would only be suitable for more stable patients and not those with more serious wounds that might require more invasive management, such as amputation.
	Acceptability	• HCPs felt that patients would appreciate the convenience of managing their wounds at home. • However, the consensus is that they might face more resistance from elderly patients, who were not so open to using technology.

	Compliance	• HCPs felt that the application might suit individuals who were more compliant and technology savvy but not for individuals who were more nonchalant about their condition.
Perceived barriers for HCPs	Compatibility with electronic medical records (EMRs)	• HCPs were concerned about integrating the application with the hospital's EMRs, which might lead to wasted time.
	Wound image quality	• HCPs were concerned about how the angle or lighting might affect the wound image quality and, consequently, the overall accuracy of the analysis. • One HCP stated that the wound image might not be an accurate representation without prior cleaning and debridement.
	Cost	• Many HCPs were concerned about the application cost and whether it would be borne by the healthcare institution or the patient.

Chapter 12: Digital Health: Feasibility Study on the Efficacy of a Patient-Owned Wound Surveillance System for DFU Care (ePOWS Study)

Summary

Building upon the findings from Chapter 11, we tailored a DFU wound application suitable for implementation in the local population. In addition, we conducted a novel feasibility study on the efficacy of a patient-owned wound surveillance system for DFU care in the community. We conducted a two-institutional, prospective, single-arm pilot study on patients with foot wounds after DLS discharge. An artificial intelligence-enabled image analysis application was installed. Patients or caregivers were instructed to take pictures of wounds during dressing changes. The primary outcomes included the incidence of wound deterioration, wound healing, and wound stability at 6 months. The secondary outcomes included study adherence and user experience. From January 2021 to December 2021, 39 patients were enrolled in the study. Usage of the application for surveillance of DFU healing yielded a sensitivity of 100%, specificity of 20%, positive predictive value of 83%, and negative predictive value of 100%. The study completion rate was 64% (n = 25). Of those who provided user experience feedback, 47% (n = 8) would recommend the wound analysis application to others. However, only 6% would pay for the application out of pocket (n = 1). In conclusion, the implementation of a patient-owned wound surveillance system is feasible. Most patients effectively monitored wounds using a smartphone application-based solution. The image analysis algorithm demonstrated strong performance in identifying wound healing. It could detect deterioration before interval evaluation by a physician.

Methodology

This two-institutional, prospective, single-arm pilot study recruited patients from two tertiary hospitals in Singapore (800- and 1,300-bed hospitals). Patients were recruited for the study if they (1) were older than 21 years, (2) were able to provide informed consent, (3) were discharged from a participating institution with an active wound at or below the level of the ankle, (4) were scheduled for follow-up at a participating polyclinic or for home wound management, (5) owned a smartphone compatible with application function, and (6) were personally, or had a carer who was, able to train in the use of eKare. Pregnant and breastfeeding women were excluded from this study.

The eKare InSight application (eKare Inc., Fairfax, VA) (eKare or the application) was used to monitor wound healing. It uses machine learning-driven wound imaging analysis on mobile phone images to model wound dimensions *via* digital planimetry [57-58]. eKare was customized for the study population according to the stated preferences of patients, carers, and HCPs, as elucidated in Chapter 11. Features included offline access, interfaces in local languages, and push notifications to physicians as requested by patients and carers. A compiled dashboard of findings, integrated subjective wound questionnaires for infection-related symptoms, and health records were incorporated for HCPs [59].

The study participants installed the application on their personal devices. They were trained on how to use the eKare tool before the study. Each training session concluded with the successful independent capture of a wound image by the patient or caregiver.

Baseline demographic information, medical history, medical management, and wound characteristics were collected from patient health records. Further demographic and functional information was collected using the Client Service Receipt Inventory questionnaires (Appendix 8).

After discharge, the participating patients were instructed to perform home dressing changes and attend outpatient wound care appointments as outlined in the discharge instructions. They were instructed to take a picture of their wounds during each dressing change. Participating individuals were followed up until they experienced a primary outcome (whichever earlier) of either (1) wound deterioration, as defined by increasing wound surface area when measured by eKare, or infection requiring admission, antibiotic therapy, or surgical intervention; 2) wound healing; or 3) stable wound status after 6 months. The increase in wound area measured by the application was verified by a physician at the subsequent appointment. Secondary outcomes included (1) adherence to the study protocol and (2) user experience as measured by ratings and comments collected at the end of the study.

Institutional Review Board approval was granted (NHG 2020/01348), and written consent was obtained from each enrolled patient. Statistical analysis was performed using R Version 4.2.3 and RStudio Version 2023.03 software (PBC, Boston, MA). Continuous variables were presented as mean value ± SD. Discrete variables were presented as values with percentages of the relevant population as appropriate. Descriptive and continuous values were compared using chi-squared and *t* tests as applicable. *P* values ≤ 0.05 were considered statistically significant.

Results

Between January 2021 and December 2021, 39 patients were enrolled in this study. The average age of subjects in the cohort was 61.6 ± 8.6 years, and 69.2% (*n* = 27) of the participants were male. A summary of the demographics is shown in Table 42. All study participants (*n* = 39) had known diabetes diagnoses, of whom 94.9% (*n* = 37) were treated pharmacologically with a mean HbA1c level of 8.8 ± 2.5% at enrollment. Exclusive of diabetes, the most prevalent comorbidities included hypertension in 84.6% (*n* = 33), coronary artery disease in 48.7% (*n* = 19), and CKD in 46.2% (*n* = 18), with 44.4% (*n* = 8) on dialysis. A summary of comorbidities is shown in Table 42.

Of the 39 participants, 84.6% (*n* = 33) had documented PAD at enrollment, of whom 75.8% (*n* = 25) received antiplatelet and statin therapies. The mean ipsilateral toe brachial index at enrollment was 0.58 ± 0.29. Of the total cohort, 61.5% (*n* = 24) underwent ipsilateral revascularization before commencing the study. Of these 24 revascularizations, 58.3% (*n* = 14) occurred within 1 month of study involvement. Most of these revascularizations, 95.8% (*n* = 23), were endovascular, while the case was an open lower extremity bypass. Of the total cohort of 39 individuals, 10.3% (*n* = 1) underwent a contralateral major amputation before study enrollment.

All 39 patients were followed up for one primary wound (mean wound bed size 6.4 sq-cm, range 2.3-25.8 sq-cm). Additionally, secondary wounds were noted in 20.51% (*n* = 8) of individuals. The most common wound locations included sites of recent minor amputations in 69.2% (*n* = 27), toes in 15.38% (*n* = 6), and heels in 7.7% (*n* = 3). Most wounds, 61.5% (*n* =

24), were superficial and did not extend beyond the dermis. The remaining 38.4% (*n* = 15) were deep in the dermis. Thirty-nine subjects, 51.3% (*n* = 24), were on empiric antibiotic regimens. A summary of the wound characteristics is shown in Table 43.

During the study period, 35.9% (*n* = 14) of the 39-individual cohort withdrew, yielding a 64.1% (*n* = 25) completion rate. The mean follow-up for those completing the study was 12.0 ± 8.5 weeks. Of the 14 patients who withdrew from the study, 64.2% (*n* = 9) were unable or unwilling to follow the study protocol, 21.4% (*n* = 3) cited personal reasons for withdrawing, and 14.2% (*n* = 2) had mobile phones of insufficient capability. The completed cohort had a lower rate of deep wounds (24.0% *vs*. 64.3%, *P* = 0.01). Otherwise, the characteristics of the two cohorts did not statistically significantly differ.

Of the 25 patients who completed the study, 80.0% (*n* = 20) healed their primary wounds, and 20.0% (*n* = 5) experienced wound deterioration, as determined by physicians during follow-up appointments. Participants with healed wounds achieved this outcome after a mean of 9.5 ± 8.2 weeks. Figure 21 demonstrates the survival curve for wound healing. Of the 20 healed primary wounds, eKare correctly classified wound healing in all cases. Of the five deteriorated primary wounds, eKare correctly classified wound deterioration in 20.0% (*n* = 1) before physician classification. When used for detecting wound healing among the 25 patients who completed the study, the application had a sensitivity of 100%, specificity of 20%, positive predictive value of 83%, and negative predictive value of 100% (Table 45). A summary of the test performance for detecting wound healing is shown in Tables 44 and 45. A Kaplan–Meier representation of wound deterioration events is shown in Figure 21.

Of the 25 individuals who completed the study, 68.0% (*n* = 17) provided feedback on user experience after concluding the study. Of those 17 individuals, 58.8% (*n* = 10) reported finding the application interface somewhat or very easy to use (Table 46). Of those 10 individuals, 71.4% (*n* = 5) cited personal difficulties using smartphones generally, and 57.1% (*n* = 4) reported asking another individual to photograph them. Of those who completed the survey, 47.1% (*n* = 8) would recommend the application to others, 17.6% (*n* = 3) would not recommend it, and 35.3% (*n* = 6) were unsure (Table 47). Those who were unsure cited the absence of a physician's involvement as the reason for their ambivalence. Notably, those with wound deterioration were less likely to recommend the application than those whose wounds healed (0.0% *vs*. 66.7%, $P = 0.04$), although the sample size was small. Of the 17 individuals providing feedback, 5.9% (*n* = 1) stated they would pay for the application's functionality, 70.6% (*n* = 12) stated they would, and 23.5% (*n* = 4) were unsure. Those who were unsure cited the prospective cost of the application as their primary decision variable. A summary of user experience findings is shown in Tables 46 and 47.

Table 42: Summary of cohort baseline characteristics.

	Completed (n=25)	Withdrawn (n=14)	Total (n=39)	*P* value
Demographics				
Age (years)	62.3 ± 9.0	58.0 ± 5.7	61.6 ± 8.6	0.27
Female sex	32.0% (8)	28.6% (4)	30.8% (12)	0.82
Ethnicity				0.31
Chinese	40.0% (10)	21.4% (3)	33.3% (13)	
Malay	32.0% (8)	50.0% (7)	38.5% (15)	
Indian	28.0% (7)	21.4% (3)	25.6% (10)	
Other	7.1% (1)	0.0 % (0)	2.6% (1)	
Medical history				
A1C	8.6 ± 2.4	9.1 ± 2.9	8.8 ± 2.6	0.56
Smoking				0.20
Active	8.0% (2)	28.6% (4)	15.4% (6)	
Prior	16.0% (4)	7.1% (1)	12.8% (5)	
Never	76.0% (19)	64.3% (9)	71.8% (28)	
Peripheral vascular disease	84.0% (21)	85.7% (12)	84.6% (33)	0.89
Toe Brachial index	0.57 ± 0.32	0.61 ± 0.23	0.58 ± 0.29	0.71
Hypertension	88.0% (22)	78.6% (11)	84.6% (33)	0.43
Coronary artery disease	52.0% (13)	42.9% (6)	48.7% (19)	0.58
Chronic kidney disease	44.0% (11)	50.0% (7)	46.2% (18)	0.72
Prior stroke	20.0% (5)	7.1% (5)	15.4% (6)	0.29
Subjective health score (1–100)	61.3 ± 21.1	56.4 ± 21.6	59.6 ± 21.1	0.50

Table 43: Summary of wound characteristics.

	Completed (n=25)	Withdrawn (n=14)	Total (n=39)	*P* value
Mean wound bed size, sq-cm (Range)	6.8 (3.4-25.8)	6.3 (2.3-18.4)	6.4 (2.3-25.8)	0.49
Location				0.39
Amputation site	64.0% (16)	78.6% (11)	69.2% (27)	
Toe	20.0% (5)	7.1% (1)	15.4% 6)	
Heel	8.0% (2)	7.1% (1)	7.7% (3)	
Plantar	8.0% (2)	0.0% (0)	5.1% (2)	
Malleolus	0.0% (0)	7.1% (1)	2.6% (1)	
Depth				**0.01**
Superficial	76.0% (19)	35.7% (5)	61.5% (24)	
Deep	24.0% (6)	64.3% (9)	38.5% (15)	
Dressing				**0.01**
Bandage	76.0% (19)	35.7% (5)	61.5% (24)	
Negative pressure	24.0% (6)	64.3% (9)	38.5% (15)	
Secondary wounds	16.0% (4)	28.6% (4)	20.5% (8)	0.35
Surgical debridement	64.0% (16)	85.7% (12)	71.8% (28)	0.15
Empiric antibiotics	44.0% (11)	64.3% (9)	51.3% (20)	0.22
Pain score (1–10)	2.5 ± 2.7	1.5 ± 2.0	2.2 ± 2.5	0.22

Table 44: Wound application usage outcomes.

		Physician		Total
		Healing	**Deterioration**	
Algorithm	**Healing**	20	4	24
	Deterioration	0	1	1
Total		20	5	

Table 45: Wound application performance characteristics.

Characteristics	Performance
Sensitivity	100.0%
Specificity	20.0%
Positive predictive value	83.3%
Negative predictive value	100%

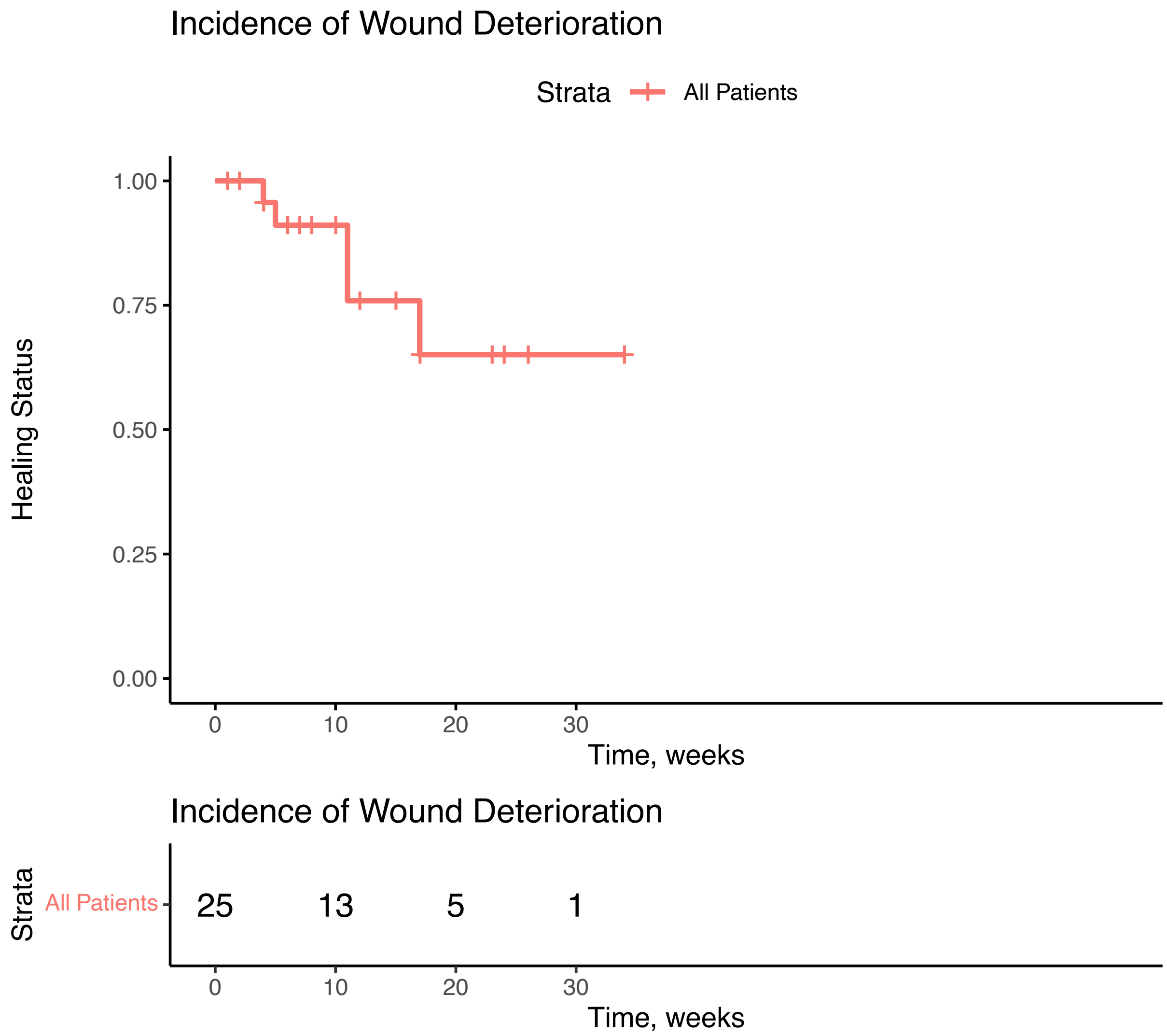
Table 46: Summary of qualitative ease of use.

Very easy	23.5% (4)
Somewhat easy	35.3% (6)
Somewhat difficult	29.4% (5)
Very difficult	11.8% (2)

Table 47: Summary of qualitative willingness to recommend and pay.

	Willingness to recommend	Willingness to pay
Would	47.1% (8)	5.9% (1)
Unsure	35.3% (6)	23.5% (4)
Would not	17.6% (3)	70.6% (12)

Figure 21: Kaplan–Meier curve for wound deterioration.



Chapter 13: Discussions

Research Question 1: What is the clinical and economic burden of DFU in Singapore?

Regardless of comparison metrics, Singapore has significantly higher DM-related major LEA as compared to other countries. In 2017, the major amputation rate in Singapore for people with diabetes stand at 95.0/100,000 [60]. When compared against Hong Kong, which has a healthcare system similar as Singapore, the major amputation rate in Hong Kong for people with diabetes was 37.5% lower at 59.4/100,000 in 2016 [61]. When compared against Denmark, which has a Gross Domestic Product (GDP) similar as Singapore, the major amputation rate in Denmark for people with diabetes was 44.0% lower at 53.2/100,000 in 2017 [62]. Similar to global data, we demonstrated a substantial clinical and economic burden of DFU within our hospital and public healthcare cluster for retrospective (Chapter 2) and prospective DEFINITE (Chapter 5) data. In an earlier study on the burden of chronic wounds within our healthcare cluster, for patients with neuroischemic ulcers (NIU), the direct healthcare cost per patient for hospital care (inpatient and specialist outpatient) and primary care in 2017 was US$16,920, with 30.5% of patients requiring two or more NIU-related admissions [63]. Building on this initial evaluation, which provided a broad overview of the burden of DFU, we presented the clinical and economic analysis of the largest longitudinal cohort of patients with DFUs to date, with Faglia's Italian series of 993 patients as the next largest single-centered series [64].

Similar to the global prevalence of DFU, we reported a more significant proportion of patients with DFUs who were elderly and male (Chapters 2–10). A higher proportion of male patients with DFUs had been consistently reported from developed [65] and developing countries [66-67], with a possible hypothesis in the gender difference owing to increased physical work in males [68]. Furthermore, the patient population analyzed showed a high percentage of patients with Malay Indian ethnicity (Chapters 2 and 5), consistent with an earlier 2008 study examining the epidemiology of diabetic foot problems in another Singapore hospital [69] and other local series [70-71]. Nather et al. reported a significantly increased incidence of diabetic foot problems in patients of Indian descent. This is likely secondary to the higher prevalence of diabetes among Indians within the local Singapore population [69]. When investigating national trends of DM-related LEA, a similar higher rate of DM-related amputations was observed among the Malay and Indian ethnicities, corresponding to their higher prevalence of DM (16.5% and 16.3%, respectively), compared to 11.2% among the Chinese [72]. Whether the variation in DRLEC was a true reflection of differential risk between ethnicities or resulted from differences in sociocultural preferences of management and health utilization remains unclear. Interestingly, the analysis of the primary care catchment population conducted in Chapter 10 revealed that although the youngest patients were from the northern catchment, it had the highest proportion of Malay and Indian ethnicities, with the highest proportion of active smokers, highest level of mean HbA1c, and high prevalence of ESRF. Consequently, patients from the north of Singapore had the highest rates of minor and major LEAs with the shortest mean days from enrollment to minor and major LEAs, coupled with the highest mean inpatient admissions. Perhaps more patient education, engagement, and empowerment efforts toward these at-risk groups should be further strengthened.

Patients within our study population demonstrated poor glycemic control, with a significant proportion suffering from macro (IHD, stroke, ESRF, and PAD) and micro (diabetic retinopathy and peripheral neuropathy) vascular complications (Chapters 2–3 and 5–10) and high DCSI [73]. In a meta-analysis of six studies involving 109,933 patients, Zhou et al. reported that the OR for the LEA incidence was 1.229 (95% CI: 1.169–1.292) for every 1% HbA1c increase [74]. In particular, for each 1.0% increase in HbA1c, the daily wound-area healing rate decreased by 0.028 cm^2/day (95% CI: 0.003, 0.0054, $P = 0.027$) [75]. Regarding glucose control, a recent meta-analysis of 47 studies ($n = 12{,}604$) reported an elevated risk of LEA with an increased HbA1c level >8% (OR 4.80, 95% CI 2.83–8.13) [76]. As a result of poor glycemic control, it was unsurprising that each patient within our study population exhibited a mean of 6.1 documented wounds within the 5-year study period.

Multivariate analysis revealed that a history of minor amputation in the preceding 12 months was an independent predictor of major and minor amputations within the 18-month study period (HR 3.4 and 1.8, respectively, $P < 0.001$). According to the local Appropriate Care Guide for foot assessment in people with diabetes, a history of previous minor amputation stratifies the patient into a high risk for future DFU development. Hence, they should have regular DFS every 3–4 months [46]. This screening is vital given that 40% of patients have DFU recurrence within 1 year after ulcer healing, almost 60% within 3 years, and 65% within 5 years [2]. A healed DFU is analogous to cancer in remission, and close surveillance is mooted [29]. Within DEFINITE Care, scaling up the DM Foot STEP program from two to all seven polyclinics for high-risk patients with DM ensures early identification, early treatment, and rapid referral of patients with DFUs to hospital-based LEAPP clinics. DFS is usually performed by the doctor looking after a patient's DM care and hence right siting of care for regular DFS according to risk stratification is especially important for patients whose primary diabetes physician is outside our polyclinic network. In addition, improvement in the health literacy of patients and carers on "Foot Attack" symptoms, diabetes control, foot self-examination, and offloading therapeutic footwear is effective in preventing up to 60%–75% of DFU recurrence [2]. This is also the impetus within DEFINITE to standardize and encourage quarterly DFS for patients with healed DFUs (Appendix 2) in accordance with Singapore's local guidelines [46]. Most DFUs occur on the toes or plantar region. In a review of 19 compatible studies on incidence rates for DFU recurrence, Armstrong et al. estimated that 40% of patients have DFU recurrence within 1 year after ulcer healing, almost 60% within 3 years, and 65% within 5 years [2]. Within the multicenter prospective Eurodiale study, significant independent predictors for recurrence were plantar ulcer location, the presence of osteomyelitis, HbA1c > 7.5%, and CRP > 5 mg/L [65]. Hence, a holistic approach of home monitoring of foot temperature, pressure-relieving therapeutic footwear, and certain surgical interventions may effectively prevent up to 60%–75% of DFU recurrence [2-3].

Concerning mortality rates, the literature stated that 5-year mortality rates were estimated at 45%, 18%, and 55% for neuropathic, neuroischemic, and ischemic ulcers, respectively [77]. Similarly, for patients who underwent minor and major LEAs, 5-year mortality was estimated at 46% and 57%, respectively, comparable to the 5-year pooled mortality rates for all-reported cancer at 31% [17]. Within our study population, the overall 5-year mortality was 37.9%, with subgroup analysis showing higher mortality signals among patients who underwent major amputations, were elderly, and had PAD, IHD, previous stroke, and ESRF. Patients with DFUs were elderly, had a longer diabetic duration, and had more hypertension, diabetic retinopathy, and smoking history than patients without DFUs. In addition, earlier data from our institution revealed that patients with NIU had multiple comorbidities and were the frailest group [71]. Globally, during 1990–2016, the age-standardized years lived with disability rates of all DRLECs increased by 14.6%–31.0% from the 1990 estimates. DRLECs were a significant and growing contributor to the disability burden worldwide and disproportionately affected males and middle-aged to elderly populations [4]. Notably, contemporary data on a 5-year follow-up on patients with DFUs from 2009 to 2010 in France [78] showed lower-than-expected mortality rates, indicating that, with increasing awareness, adherence to international guidelines, and an MDT approach, progress has been and can be made in the management of patients with DFUs, as demonstrated in Chapter 6.

In Singapore, the cost of DM was estimated at US$700 million (SG$1 billion) in 2010. This figure is projected to rise to US$1.75 billion (SG$2.5 billion) by 2050 [79]. The cost per working-age person with diabetes in Singapore is projected to increase from US$5,400 (SG$7,678) in 2010 to US$7,423 (SG$10,596) in 2050 [80]. This study reported that the mean healthcare cost for hospital (inpatient and outpatient) DFU care was US$6,615,437 (SG$9,381,748) per year, with the respective mean cost per patient-year for ulcer-only, minor LEA, and major LEA at US$3,368 (SG$4,776), US$10,468 (SG$14,845), and US$30,131 (SG$42730). These data are similar to those from the US. In 1998, the total direct cost of healing infected DFUs not requiring amputation was estimated at US$17,500 per patient. In contrast, the cost for LEAs, depending on the level of amputation, was US$30,000–$33,500 per patient [81]. In a patient with DFU, the potential economic benefits of MDT strategies were estimated as US$2,900–$4,442 per patient over 3 years [81]. Similarly, within our study population, the mean cost difference per patient-year between ulcer-only and minor amputation was US$7,100. However, the difference between minor and major amputations was US$19,663. When compared with other diseases, the direct costs of care for patients with DRLEC are comparable with those of cancer [17]. In 2017, the direct cost of care for diabetes in the US was estimated at US$237 billion, with up to one-third attributed to the lower extremity, whereas the direct cost of care for cancer in 2015 was estimated at US$80 billion [17]. Therefore, active measures to prevent DFU will help decrease the economic burden of diabetic foot disease. Evidence- and guideline-based management of DFU improves survival, reduces DRLEC, and is cost-effective compared to standard care [82]. In Chapter 6, for DEFINITE patients, healthcare utilization shifted from inpatient to outpatient care, with a reduction in mean hospital admission by 0.9, cumulative LOS by 5.5 days, and a corresponding increase in primary care visits by 1.2 and hospital specialist clinic visits by 2.8. However when compared with the control group, DEFINITE had net negative direct healthcare cost savings of US$1,769 (SG$2,400) per patient, 270 deaths were prevented, with cost savings per death prevented at US$18,057 (SG$24,498).

<u>Research Question 2:</u> How to improve outcomes of patients with DFUs through coordinated MDT care between primary and tertiary care?

Chapter 3 describes the first study from an Asian population that comprehensively evaluated the clinical and economic outcomes of an MDT approach in LEA prevention for DFU management. MDT management of DFU is associated worldwide with the best outcomes in terms of limb preservation, with most data derived from Western societies [83-88]. The National Institute for Health and Care Excellence [47] and IWGDF guidelines [30] recommended an MDT approach for DFU management as the standard of care. In Singapore, data spanning from 2002 to 2007 revealed that an MDT approach with the implementation of a clinical pathway effectively reduced average inpatient LOS, major amputation rates, and diabetic foot complications [89]. In an earlier study, 10 years ago at the same institution, a similar LEAP inpatient program resulted in a lower LEA rate of 29%, compared to the pre-LEAP cohort ($P < 0.001$), with a lower related death rate (1% *vs*. 19%, $P < 0.001$), fewer in-hospital days per patient (17.8 *vs*. 23.16 days, $P = 0.048$), and generated cost savings of US$1,912 (SG$2,566) per patient during admission [90]. However, due to workforce and administrative limitations, the resource-intensive MDT approach was halted for the past 10 years and only reinstated in its current format since December 2017 to push toward the goal of providing a rapid and efficient way to deal with the complex and relentless nature of DFU, henceforth minimizing DFU-related major amputations. Scaling up these benefits across the other tertiary hospitals within our healthcare cluster and in collaboration with our seven primary care polyclinic networks, we can now demonstrate sustained benefits within our catchment population through interinstitutional MDT DFU care, with a significant decrease in minor and major LEA rates and improved cardiovascular profile (glycemic and lipid control).

Chapter 4 describes the methodology behind the development of DEFINITE Care, a health systems innovation. According to the World Health Organization, the term “Health Systems” refers to all organizations, institutions, and resources devoted to producing actions whose primary intent is improving health [91]. “Quality improvement” (QI) is defined as systematic, data-guided activities designed to bring about immediate improvements in healthcare delivery in particular settings as an intrinsic part of normal healthcare operations. Consequently, “health systems innovation” is defined as QI in addition to novel activities, which may be the development of new products or services that produce better health or experience of care at equal or lower costs [91]. Within DEFINITE Care (health services innovation), we aim to improve the delivery of coordinated DFU care (QI) through innovations in care delivery workflow, care coordination, and wound imaging technology (Figure 12).

A proposed theoretical framework that supports the research on health service innovation involves organization, workforce, innovation-specific, financial, and political factors [92]. Within DEFINITE Care, there was buy-in and enthusiasm among multiple subspecialty colleagues across primary and tertiary care to adopt guideline-based MDT care for patients with DFU. Funded by the public healthcare cluster's Population Health Grant, we had the resources to provide for the required workforce, especially DFC and podiatrists. Accordingly, we adopted an expedited and coordinated workflow for patients with DFUs, in addition to wound imaging technology. This is based on existing national efforts on the "War on Diabetes" [40], which provided senior management buy-in and endorsement. Based on this framework, our vision is to build a comprehensive ecosystem for patients with DM foot disease, whereby for patients with at-risk foot, their risk-stratified DM Foot STEP program of DFS and FS at primary care can help with preventative care, education, and foot protection. Patients with active DFUs will receive fast-track escalation of MDT care from primary care to hospitals through the LEAPP clinics, with subsequent shared wound care while maintaining a foot in remission. These are underpinned by the continual engagement and empowerment of patients and healthcare providers (Figure 12).

Through DEFINITE Care, involving medical and surgical disciplines with a nuclear team "captained" by passionate institutional leads and supported by ancillary team members, we implemented, across the healthcare cluster, a comprehensive risk-stratified DFS surveillance system (STEP program), clear referral algorithms from primary care to tertiary institutions, MDT LEAPP clinics at hospitals, MDT inpatient care pathways and coordinated comanagement care between primary care (regular wound dressings, diabetes control, and patient/carer education), and tertiary care (revascularization, surgical wound care planning, and offloading) after discharge from inpatient DLS procedures. This has enabled timely, comprehensive, and coordinated DFU care between primary and tertiary care while ensuring the optimization of diabetes control and patient/carer education.

In a systematic review of the efficacy of MDT in reducing major amputations for patients with DFU, four essential team-related elements identified included teams comprising medical and surgical disciplines, larger teams benefiting from having a "captain" with a nuclear and ancillary team structure, clear referral pathways, and care algorithms supported by timely and comprehensive care [50]. Within LEAPP (Chapter 7), we have the vascular surgeons "captaining" the team, with active input from endocrinologists, podiatrists, and wound nurses, thus forming the nuclear team structure. Ancillary team members include orthopedic surgeons, infectious disease physicians, prosthetics and orthotic technicians, and plastic and reconstructive surgeons. All patients with preexisting DM and referred for foot ulcers (distal to malleolus) are seen in LEAPP clinics, with referrals screened by a vascular surgeon three times a week. Similar to the four key tasks identified in the systematic review, our MDT approach focuses on metabolic profile optimization, local wound management, revascularization, and infection control. Hence, similar to 94% (31/33) of studies within the systematic review [50], which reported a reduction in LEA after the institution of an MDT approach, a significant decrease was observed in 1-year minor amputation rates within the LEAPP cohort (14% *vs*. 3%, $P = 0.007$), as well as a decrease in major amputation rates within the LEAPP cohort (9% *vs*. 3%, $P = 0.05$). At 1 year, DEFINITE had a significant 5.5%

improvement in minor LEA-free survival and 9.0% improvement in major LEA-free survival with longer mean days from enrollment to minor LEA, major LEA, and death.

The involvement of podiatry in MDT DFU management is crucial. In our study cohort, we observed a significant increase in outpatient podiatry follow-up (33% *vs*. 76%, $P < 0.001$) for LEAPP patients. Having podiatry within the MDT clinic provides prompt wound care and offloading, thereby improving the adherence of patients to podiatry follow-up appointments. Unlike the retrospective cohort in which patients had to attend a separate podiatry clinic appointment, this "one-stop" MDT clinic provides convenience for patients with DFUs, indirectly saving the time and transport of patients and their caregivers. A systematic review and meta-analysis on the effect of podiatry in a team approach for DFU and LEA reported that the inclusion of podiatrists within the MDT significantly and positively affected patient outcomes in terms of total LEAs and major LEA [93]. Management of DFU involves complex wound- and vascular-related interventions and appropriate custom-made footwear and offloading insoles. These interventions effectively treated DFU and prevented its recurrence [94], which stands at 40% within 1 year [2].

<u>Research Question 3:</u> With coordinated MDT care between primary and tertiary care, what are the clinical and economic outcomes for patients with DFU?

A recent 10-year retrospective study investigating 156,593 local patients with type 2 DM revealed a rapid progression of 2.3 months from DRLEC to the first amputation [95]. This underscores the importance of having a diabetic foot care pathway and a coordinated foot care service for diabetic patients. Within our study, upon the commencement of the MDT LEAPP clinic, a significant decrease was observed in the meantime from referral to index clinic visit (38.6 *vs*. 9.5 days, $P < 0.001$). In addition, a significant decrease was detected in the mean time from the index visit to vascular diagnostic imaging and revascularization (24.2 *vs*. 9.9 days, $P < 0.001$, and 39.0 *vs*. 32.6 days, $P = 0.015$, respectively). Patients with DFUs and chronic limb-threatening ischemia will benefit from earlier imaging and vascular intervention, as evidenced by higher limb salvage rates. The coordinated and MDT approach allowed for DFU-related healthcare providers, such as vascular surgeons, endocrinologists, podiatrists, and wound nurses, to provide a continuum of care from the outpatient clinic to admission and subsequently after inpatient discharge back to outpatient postoperative care in a process that allows seamless care of complex diabetic foot wounds and provides holistic care in terms of diabetic control, footwear optimization, and patient education. Consequently, patients within the LEAPP subgroup analysis (Chapter 7) had a significantly lower risk of death (OR 0.60, $P = 0.001$) and composite major LEA/death (OR 0.66, $P = 0.002$) at 1 year, with longer mean days from enrollment to minor LEA, major LEA, and death. In terms of healthcare utilization, the adjusted 1-year outcomes for LEAPP patients were an increase in inpatient admissions with an associated decrease in cumulated LOS, a rise in primary care polyclinic visits, and an escalation in hospital SOC visits and elective day surgery procedures. Our LEAPP clinic focuses on optimisation of metabolic profile, wound management, revascularisation, and infection control[15]. Patients are reviewed regularly at our tertiary LEAPP clinic, generally 2-4 weekly to ensure infection control and optimisation for wound healing. In between visits to the LEAPP clinic, patients are seen regularly at primary care for wound review and dressing changes. Additionally, the LEAPP clinic allows timely and rapid access to revascularisation procedures. These factors partially explain the increased healthcare utilisation in day surgery, polyclinic and SOC visits. However, as demonstrated also by the LEAPP subgroup analysis (Chapter 7), only 1 in 5 within the DEFINITE cohort (20.6%) flowed through our MDT LEAPP clinics at both tertiary hospitals. This is likely secondary to a significant proportion of patients who have their primary care managed outside of the healthcare cluster's polyclinics network (49.8%). Further refinement of the referral workflow and review of the implementation science methodology will be performed beyond this current study.

In terms of minor and major LEA rates from the retrospective cohort (Chapter 2) and prospective DEFINITE cohort (Chapters 5 and 6), a significant improvement was noted in minor and major LEA-free survival rates of 5.5% and 9.0%, respectively. Earlier studies have identified multiple risk factors for LEAs, including age, infection, PAD, IHD, and ESRF. In the US, up to 20% of moderately or severely infected DFU eventually lead to amputation [17]. PAD independently increases the risk of nonhealing ulcers, infection, and LEA. Similarly, within Asia, data from the Japanese OLIVE registry revealed that age, BMI, ESRF, and Rutherford grade 6 classification were identified as predictors of major amputation or death [96]. Within patients of Chinese ethnicity, the overall amputation rate among DFU cases was 21.5%, with stepwise logistic regression analysis revealing PAD as one of four significant risk factors [97]. Traditionally, ESRF patients have a higher risk of limb loss after revascularization and poor survival [18]. Furthermore, previous LEA was an independent predictor of subsequent minor and major LEAs within our retrospective cohort. In the literature, mortality after DFU-related major LEA exceeded 70% at 5 years, with mortality rates even higher at 74% at 2 years for patients with ESRF [77-78]. However, whether such high mortality rates result from a combination of premorbid conditions (including amputation perioperative risks), lack of activity, or deconditioning remains unclear.

When comparing results from the retrospective cohort against prospective DEFINITE cohort, PSM allowed the adjustment of known risk factors, and we demonstrated a significant reduction in mortality rates. The unadjusted rates of minor LEA had increased, whereas the absolute rates of major LEA had been static. With a reduction in mortality rates, more DLS was performed were within the program, hence increasing the absolute minor LEA rates. Within DEFINITE Care, improvement in glycemic control can be attributed to increased endocrinology input at inpatient care and outpatient MDT LEAPP clinics. In addition, there is continuity of care beyond the acute DLS episode, where patients receive closed-loop care coordination between hospitals and polyclinics after an inpatient discharge. This improvement in the cardiovascular risk profile is pertinent given the higher mortality in individuals with DFUs ascribable to a higher cardiovascular burden. With improved metabolic control and DLS procedures, a reduction was observed in the overall mortality rates, thereby improving minor and major LEA-free survival composite outcome measures.

An integrated and structured approach to managing DFU can reduce DFU-related complications, infections, amputation rates, and mortality rates [98-99], translating into reduced economic and patient costs [100-101]. However, although proven to have improved clinical outcomes, the labor- and resource-intensive MDT care model for DFU is costly, and reimbursement may be inadequate [36]. Increasing evidence indicates that the costs of implementing DFU teams may be offset in the long run by improved access to care and reductions in foot complications and amputation rates. In New Zealand, the implementation of an MDT foot care team reduced major amputation rates (3.8% *vs*. 27.5%, $P < 0.001$), mortality rates (7.5% *vs*. 19.2%, $P < 0.05$), and costs associated with DFU wound episodes by 25%

[49]. Although when compared with the control group, DEFINITE had a net negative direct healthcare cost savings of US$1,769 (SG$2,400) per patient, 270 deaths were prevented, with cost savings per death prevented at US$18,057 (SG$24,498).

Over a 12-month study period, DFU patients within DEFINITE Care experienced an improvement in HRQoL across almost all domains assessed (Chapter 6), suggesting that patients learn to accommodate their healed or non-healed DFUs when performing activities of daily living. Regarding ulcer healing, healed ulcers demonstrated improvements in all domains and had better HRQoL scores as compared to ulcers that did not heal during the 12 months assessed. Other studies have reported equivalent findings: in a cohort of 294 patients, healing of DFUs resulted in a marked improvement in SF-36 while HRQoL declined amongst non-healed ulcers [102]. Less reliance on off-loading devices, decrease in pain sensation and reduced need for wound management may be some of the reasons why healed ulcers are associated with higher HRQoL [103-104].

<u>Research Question 4:</u> What are the characteristics and outcomes for at-risk subgroup populations?

Chapters 8 (defaulters), 9 (octogenarians) and 10 (primary care catchment population) analyzed the characteristics and outcomes of various at-risk subgroup populations. Concerning treatment adherence, DEFINITE results (Chapter 5) demonstrated a low DFS rate, especially among at-risk patients with DM. Although the Agency for Care Effectiveness provided an Appropriate Care Guide for foot assessment to people with diabetes [46], which stratified patients into low, moderate, and high risks with corresponding DFS schedules of 1 year, 6 months, and 3 months, DEFINITE results showed that approximately one-third of patients who presented with DFUs would have had DFS performed in the preceding 12 months. This supports findings from an earlier publication from Singapore, which concluded that lack of diabetes foot screening, lower socioeconomic status, hip fracture, Malay ethnicity, CKD, poorer glycemic control, longer diabetes duration, and male gender are associated with a higher risk of LEA [105]. In addition to the low DFS rates among the DEFINITE population, there was a high defaulter rate of more than 40% (Chapter 8). These patients were younger males of Malay and Indian ethnicities and ex-smokers/current smokers, with fewer comorbidities but worse DM control with poor HbA1c levels. They had DM retinopathy despite being on DM medications. Previous studies have reported that patients who defaulted on treatment consistently presented with significantly worse outcomes, regardless of intervention or disease [106]. Within the realm of DM foot care literature, there are heterogeneous findings regarding factors affecting patient adherence. In a systematic review and classification of factors influencing DFU treatment adherence, our group found that the largest proportion of factors studied was patient-related, such as patient insight on DFU treatment, patient motivation, and patient perception of DFU treatment. There was notable overlap in the range of discussed factors across various domains: in the socioeconomic (including social support, income, social and cultural acceptability of DFU therapy, cost) and therapy-related domains (including duration of treatment, offloading footwear, and reminder devices).

Consistent with a prior study conducted among patients who missed scheduled appointment in a nurse-led clinic [108], our study similarly found unawareness of or simply forgetting the appointment was the most common reason for nonattendance at DFU clinics. A substantial body of literature identifies multiple factors associated with poor appointment adherence among patients with diabetes, including demographic factors (e.g., younger age and minority ethnicity), clinical characteristics (e.g., higher HbA1c readings, decreased High-density lipoprotein cholesterol levels, multimorbidity, and presence of diabetic complications), medication history (e.g., having complex treatment regimens), psychosocial factors (e.g., poor mental health state, poor social support and financial problems), and healthcare system-related factors (e.g., accessibility of care) [109-114]. Amongst our study population, we identified several factors associated with nonattendance to scheduled appointments at DFU care clinics, including younger age, higher baseline HbA1c readings, and Malay and Indian ethnicities. In addition, prior studies have documented the relationship between nonadherence to appointment and poorer limb salvage outcomes. For instance, Selby and Zhang highlighted a positive association between the number of missed appointments and the odds of amputation [115]. Armstrong and Harkless reported that nonattendance to over 50% of scheduled appointments in any calendar year was associated with a higher risk of amputation [116]. In our study, defaulters had a higher minor LEA rate compared to non-defaulters. However, the difference became non-significant after adjusting for the covariates. Nonetheless, the consistently lower LEA-free survival rates among defaulters highlights the enduring impact of nonadherence to scheduled DFU care appointments on composite outcomes encompassing both LEA and mortality.

Addressing the modifiable system and patient education issues is important to holistically improve patient adherence and implement interventions targeting these risk factors. As demonstrated within our health services innovation program, establishing clear pathways for coordinated care across primary and tertiary care helps ensure easy access to specialist care, thereby creating a conducive healthcare environment to improve treatment adherence. Through digital health, such as having a patient-owned wound surveillance system, there will be seamless communication between patients and their healthcare providers and improves communication among healthcare providers, facilitating easy referral, follow-up, and shared care plans.

In terms of DLS amongst octogenarians (Chapter 9), there are contradictory findings in the existing literature. While some literature suggested that advanced age might be associated with poorer outcomes [117-118], others demonstrated that limb salvage could be achieved in older DFU patients at rates comparable to their younger counterparts, despite these patients presenting with more comorbidities and foot-related complications [119-121]. Within our study, when comparing between Octogenarians and non-Octogenarians, there is a greater percentage of female Chinese non-smokers with better DM control and lesser complications, yet having more co-morbidities. Despite more aggressive DLS efforts within DEFINITE Octogenarians, there were good outcomes of lower major LEA rate, mortality rate and longer mean days from enrolment to death Even after adjusting for age, gender, comorbidities and medications, the benefits of DLS within DEFINITE Octogenarians are consistently seen, with a transfer of inpatient care to outpatient care. The findings echo other studies that have demonstrated the favourable impact of the multi-disciplinary management approach for DFUs, both in terms of clinical and economic outcomes [122-123]. However, it is important to exercise caution when attributing the observed differences solely to the DLS programme as comparing outcomes between a current programme group and the historical control group does not account for changes in medical practices, technological advancement, and patient management which may have evolved over time. Existing collaborations between surgical and geriatric teams may also contribute towards a reduction in nosocomial complications and readmission rates [124].

In the final sub-group analysis within DEFINITE Care (Chapter 10), which assessed characteristics and outcomes according to primary care catchment population, we found a significant difference in characteristics and outcomes amongst patients from the Central and Northern catchment. Although the youngest patients were from the Northern catchment, it had the highest proportion of Malay and Indian ethnicities, with the highest proportion of active smokers, highest level of mean HbA1c and high prevalence of ESRF. Consequently, patients from the North had the highest rates of minor LEA, major LEA with shortest mean days from enrolment to minor and major LEA, coupled with highest mean inpatient admissions. In the US, racial and ethnic minorities admitted to hospitals with diabetic foot infections have a consistently significantly higher risk of major amputation and longer hospital length of stay than their White counterparts [125]. In Singapore, staying in public rental housing appears to be a risk marker of poorer health [126]. In a local retrospective study from 2007 which evaluated the socioeconomic profile of 112 diabetic patients with and without foot problems, Malay ethnicity ($p<0.001$), education of up to secondary school only ($p=0.021$), low average monthly household income of less than SGD $2,000 ($p=0.030$), lack of exercise (at least once a week, $p=0.04$), and elevated $HbA1_C$ level (>7.0%; $p=0.015$) were found to be significantly higher in the cohort with diabetic foot problems than the cohort without [127]. Given the national census depicting lower socioeconomic status and larger proportion of Malay/Indian ethnicities amongst population in the north of Singapore [43], findings from DEFINITE suggest that poor DFU-related outcomes may be correlated with social determinants of health.

<u>Research Question 5:</u> How can we leverage on technology and digital health in our care for patients with DFU?

In our qualitative study on patients, carers, and HCPs' perspectives on a patient-owned wound surveillance system for patients with DFUs (Chapter 11), the concept was positively received and perceived as feasible and effective in DFU care. Patients and carers were more focused on the benefits of convenience and potential time saved from wound imaging and remote monitoring. Healthcare providers (HCP) agreed that there are benefits of convenience and reduced waiting times. They were also excited about the possibility of sharing information with other HCPs for better continuity of care.

Furthermore, potential barriers might reduce the adoption or effectiveness of a wound imaging application. Patients and carers mostly focused on the general usability of the application, including the uptake rate among elderly patients. In our study, elderly patients with diabetes had more mobility, visual, and language barriers. Previous studies have also mentioned these challenges; hence, they should be considered during adoption [128-130]. In addition, ease of use was a key factor in previous studies. It influences the adoption rates, especially among elderly patients [131-132]. Ease of use can encourage early adoption among elderly patients who are not well-versed in technology. This can prevent early negative experiences that might deter application usage [132]. These sentiments were also echoed by HCPs. Fortunately, most of these barriers can be resolved, for example, by adding different languages and creating a more user-friendly application.

However, several barriers require workarounds. First, HCPs were concerned about image quality and whether sufficient wound assessment could be achieved by visualization alone without other factors, such as temperature or smell [133]. Second, in concordance with other studies [128], we found that some elderly patients preferred in-person interactions with their doctors and face-to-face consultations because of their flexible schedules. Therefore, they value in-person interactions with their doctors. Finally, some HCPs were concerned about integrating the wound care application into the healthcare system's EMRs for documentation and the cost of maintaining the application. Although previous studies conducted in the Canadian healthcare system have found telemonitoring a cost-effective way to manage DFU, no studies have been performed within the Singapore healthcare system [134] on this matter.

Furthermore, telemedicine in DFU care has been well-received, valid, reliable, and feasible [135-136]. Although many of these technologies remain in infancy, the COVID-19 pandemic and current unmet needs to decentralize care for patients with DFUs have accelerated the uptake of digital health, smart wearables, telehealth technologies, and the "hospital-at-home" care delivery model. These technologies can be adopted at scale to improve the remote management of DFUs by triaging those who need to be examined in outpatient or inpatient settings and supporting acute or subacute care at home [137]. Hence, if future developments can integrate this application with the national EMR system and increase uptake among local patients, patients will be empowered to monitor their wounds while having expedited clinical management when necessary. This will lead to improved patient outcomes and increased cost-effectiveness for the healthcare system.

Building on the findings from Chapter 11, Chapter 12 presents findings from the pilot clinical study, evaluating the efficacy of a patient-owned wound surveillance system for DFU care (ePOWS Study). The patient-owned aspect of clinical decision support is a unique aspect of this study compared to other uses of machine learning in healthcare. The efficacy of the semiautonomous tool was contingent upon the reliable performance of the patient. Moreover, the algorithm analyzed the information and sent it to the physician for ultimate medical management. Based on our findings, this three-way circuit among the patient, machine, and physician appears feasible.

To our knowledge, another contemporaneous pilot study evaluated a commercially available patient-owned analytic wound assessment system. Keegan et al. analyzed a similar machine-learning solution among a cohort of 25 individuals in the US [138]. Differences from our study in methodology included weekly reminder calls to patients who did not take images and technical support by phone to enrolled individuals. Although 28% of patients in Keegan et al.'s study failed to complete the study, an additional 12% of patients were categorized as unengaged, yielding a total participation deficit similar to our 36% withdrawal rate. Similar to our study, most patients who completed surveys after the study period found the interface easy to use, with 88% responding positively. Most patients in their study (94%) found the solution useful, as opposed to the 47% recommendation rate in our study. However, in concordance with our subjective user experience findings, patients in Keegan et al.'s study also commented on the lack of real-time physician feedback.

Swerdlow et al. conducted a pilot study on a patient-owned image capture system for primary care and active monitoring of pre-ulcerative and ulcerative foot wounds among 15 patients in the US [139]. The application studied was not an analytic clinical decision support system but rather a hardware solution with an accompanying software interface to capture foot wounds that patients may have missed before professional evaluation because of anatomic or patient functionality constraints. Similar to Keegan et al.'s study, patients were contacted and offered technical support if they did not submit daily photographs. All patients completed the

5-month study, and at the end of the study period, the participants gave median 10/10 maximum scores when polled on whether the application was useful and whether they would recommend the solution. Neither Swerdlow et al. nor Keegan et al. polled patients about their willingness to pay [138-139].

While the exact reasoning behind withdrawal rates may be difficult to elucidate, feedback on user experience aligns with the literature on adopting new technologies among patients. Galavi et al. conducted a systematic review of barriers to the adoption of health technology solutions in home care [140]. They found that significant barriers to entry for patients included factors such as lack of digital literacy, difficulty of use by older adults, forgetfulness, and complexity of existing comorbidities. Chapter 11 identified the apparent absence of a physician's involvement as a primary concern of patients considering the use of an artificial intelligence-enabled system.

Significantly, there is no evidence that the patient-owned treatment paradigm in this study harmed participants. Approximately 80.0% (n = 4) of the five deterioration events were identified by physicians during routine wound care. The remaining case was identified using eKare even before evaluation by a physician. Notably, in this protocol, the algorithm was used in conjunction with and not as a replacement for the standard of care by a physician. Furthermore, participants completed the study and healed their wounds in a mean of 9.5 ± 8.2 weeks. Although it is difficult to comprehensively compare the quality of wounds with those described in the literature, this time to heal is comparable to the mean 9 and 10.8 weeks described by Ince et al. and Zimny et al. [141-142].

However, four significant limitations make it difficult to measure the increase in efficacy from patient-owned wound surveillance. First, this was a single-arm pilot study designed to prove feasibility. Therefore, the lack of a control group or randomization prevents the study from proving that the patient-owned surveillance model is more beneficial than the standard of care. Second, a significant portion of the enrolled patients withdrew from the study. Although age and health status did not explain the difference between those who completed the study and those who did not, the presence of a responsible feature would influence the efficacy of this solution in the real world. Those who withdrew had a higher prevalence of deep wounds, perhaps reflecting physical limitations when taking pictures or trepidation regarding deviations in the standard of care. Third, although this model of wound monitoring is clinically and logistically feasible, a lack of cost analysis obscures whether the system is financially feasible. Patients were largely uninterested in incurring additional costs for using the eKare solution. However, increased care efficiency from patients monitoring their own wounds may return value to the system. Further work is required to quantify these effects. Fourth, no publicly available validation performance data are available for the eKare Insight system that can be compared to real-world performance data with respect to this application. Machine-learning models in the real world are expected to have impaired performance compared to their performance in controlled studies. These discrepancies can occur when the models are exposed to new populations temporally or geographically. Performance impairment can also be caused by adherence or quality of data input.

Knowledge Gaps and Focus of Future Research:

Whilst this thesis evaluated the immediate clinical and economic outcomes of health system innovations like DEFINITE Care, long-term follow-up studies could provide insights into the sustainability of these benefits, potential for further improvement, and the impact on patient quality of life over time. Investigating the role of personalized medicine, including genomics and biomarkers, in predicting DFU risk, treatment response, and healing outcomes could enhance the customization of care plans and improve patient outcomes. With regards to the implementation of digital health solutions for DFU care, future research could systematically evaluate the efficacy, patient adherence, and cost-effectiveness of various digital health technologies, including wearable devices and telehealth services, in managing patients with DFU, especially in the community. Exploring the effectiveness of various patient education and behavioural intervention models in different cultural and socioeconomic contexts within Singapore could identify best practices for improving self-management behaviours, adherence to treatment plans and overall health activation scores. Further research into the barriers to accessing DFU care, including social determinants of health and healthcare disparities among different ethnic groups or socioeconomic statuses in Singapore, could inform and enable population-based targeted interventions to improve access and outcomes. While this thesis indicates economic benefits associated with health system innovations, detailed cost-effectiveness analyses of different MDT care models (including staffing, technology, and operational costs) could help optimize resource allocation. Beyond current research scope and direction, investigating the impact of environmental and lifestyle factors, such as diet, physical activity, and urban vs. rural living conditions, on DFU incidence and healing rates could offer insights into preventive strategies. Lastly, evaluating the impact of policy changes and healthcare system restructuring on DFU management and patient outcomes could provide evidence for health policy advocacy. Addressing these knowledge gaps through future research could significantly contribute to the field of DFU management, enhancing patient care, reducing the economic burden, and ultimately improving the quality of life for individuals with DFU in Singapore and beyond.

Chapter 14: Conclusions

We performed mixed-methods research to evaluate the burden of DFU disease in Singapore and improve outcomes through health systems innovations of coordinated MDT care between primary and tertiary care. We evaluated the clinical and economic burden of patients with DFUs *via* a 5-year (2013–2017) longitudinal multiethnic cohort study at a university tertiary hospital in Singapore and our public healthcare cluster (2016–2017). Both analyses concluded that there is a significant clinical and economic burden of DFU, with most patients being elderly males with a higher likelihood of being of Malay and Indian ethnicities. They have significant comorbidities of hypertension, dyslipidemia, ischemic heart disease, CKD, and poor diabetes control. At 1 year, the minor LEA rate was 1 in 3 patients, the major LEA rate was more than 1 in 20 patients, and the mortality rate was almost 1 in 3 patients, with heavy healthcare utilization and mean direct healthcare cost per patient just under US$12,000 (SG$16,000) per year.

Pilot data on an MDT LEAPP clinic for DFU care demonstrated a significant decrease in the mean time from referral to index clinic visit (38.6 *vs*. 9.5 days, $P < 0.001$), increase in outpatient podiatry follow-up (33% *vs*. 76%, $P < 0.001$), decrease in 1-year minor LEA rate (14% *vs*. 3%, $P = 0.007$), and decrease in 1-year major LEA rate (9% *vs*. 3%, $P = 0.05$). Simulation of cost avoidance demonstrated an annualized cost avoidance of US$1.9 million (SG$2.5 million) for patients within the LEAPP cohort. Expanding on this, a multi-disciplinary and inter-institutional DFW was convened. We used mixed methods (qualitative discussions and quantitative polls) to identify existing health service deficiencies for DFU care. Referencing international guidelines and best-practice DFU-related health service literature, we tailored an institution-specific DFU program for scaling up across the healthcare cluster.

Diabetic Foot in Primary and Tertiary (DEFINITE) Care is an inter-institutional and MDT health systems innovation program at a healthcare cluster in Singapore. We aimed to achieve coordinated MDT care across primary and tertiary care for patients with DFUs within our public healthcare cluster—an integrated network of seven primary care polyclinics and two acute care tertiary hospitals (1700 and 800 beds) with a total catchment population of 2.2 million residents.

Between June 2020 and September 2022, there were 4,660 unique patients with DFUs, of whom 61.2% were male. These patients had a mean age of 65.9 years, a mean baseline HbA1c level of 8.3%, a mean diabetes duration of 13.3 years, a DCSI of 5.6, and a mean CCI of 6.8. In the 12 months preceding enrollment to DEFINITE Care, 35.5% had surgical foot debridement, 21.2% minor LEA, 7.5% major LEA, and 16.8% revascularization procedures. Multivariate analysis revealed a history of minor amputation in the preceding 12 months as an independent predictor of major and minor amputations (HR of 3.4 and 1.8, respectively, $P < 0.001$). Subsequently, we performed 1:1 PSM on patients enrolled within DEFINITE Care ($n = 2,798$, June 2020–June 2022) against a retrospective control group ($n = 5,462$, June 2016–December 2017). At 1 year, DEFINITE had a significant 5.5% improvement in minor LEA-free survival and 9.0% improvement in major LEA-free survival with longer mean days between enrollment to minor LEA, major LEA, and death. Healthcare utilization shifted from inpatient to outpatient care, with a reduction in mean hospital admission by 0.9 and cumulative LOS by 5.5 days and a corresponding increase in primary care visits by 1.2 and hospital specialist clinic visits by 2.8. In addition, DEFINITE patients had a significant improvement in DM control. Although DEFINITE had net negative direct healthcare cost savings of

US$1,769 (SG$2,400) per patient compared with the control group, 270 deaths were prevented, with cost savings per death prevented at US$18,057 (SG$24,498).

Subgroup analysis of the DEFINITE Care study population showed a significantly lower risk of death (OR 0.60, $P = 0.001$) and composite major LEA/death (OR 0.66, $P = 0.002$) among the LEAPP patients at 1 year, with longer mean days from enrollment to minor LEA, major LEA, and death. In terms of healthcare utilization, the adjusted 1-year outcomes for LEAPP patients were an increase in inpatient admissions with an associated decrease in cumulated LOS, primary care polyclinic visits, hospital SOC visits, and elective day surgery procedures. Patients who defaulted on DFU-related clinic appointments did not exhibit an increased risk of minor LEA, major LEA, or death. However, they demonstrated a significant increase in subsequent healthcare utilization for inpatient and outpatient services. In addition, between January 2021 and December 2021 ($n = 970$), we qualitatively evaluated the reasons for defaulting and categorized them into modifiable system issues (green), modifiable patient education issues (orange), changes in medical condition (red), and unmodifiable reasons (gray). Almost two-thirds (64.7%) of the reasons for defaulting were modifiable system issues (37.5%) or patient education issues (27.2%). Despite more aggressive DLS efforts within DEFINITE octogenarians, there were good outcomes of lower major LEA rate, mortality rate, and longer mean days from enrollment to death. After adjusting for age, gender, comorbidities, and medications, the benefits of DLS within DEFINITE octogenarians were consistently noted, with a transfer of inpatient care to outpatient care. Although the youngest patients were from the northern catchment, it had the highest proportion of Malay and Indian ethnicities, with the highest proportion of active smokers, the highest level of mean HbA1c, and the highest prevalence of ESRF. Consequently, patients from the north had the highest rates of minor LEA and major LEA with the shortest mean days from enrollment to minor and major LEAs, coupled with the highest mean inpatient admissions.

Utilizing digital health, concerning a patient-owned wound surveillance application, patients (*n* = 20, carers (*n* = 5), and HCPs (*n* = 20) were all open and receptive to the system and workflow for use in DFU care. Four major themes emerged from patients and carers: (1) technology, (2) application features and usability, (3) feasibility of using the wound imaging application, and (4) logistics of care. Four major themes were identified from HCPs: (1) attitudes toward wound imaging application, (2) preferences regarding functionality, (3) perceived challenges for patients/carers, and (4) perceived barriers for HCPs. When we piloted such a patient-owned wound surveillance system for 39 patients discharged from hospitals after DLS, there was a sensitivity of 100%, specificity of 20%, positive predictive value of 83%, and negative predictive value of 100% for the surveillance of DFU healing. Implementing a patient-owned wound surveillance system is feasible, and most patients can effectively monitor wounds using a smartphone application-based solution.

In conclusion, Singapore faces a substantial clinical and economic burden of DFU. Through a health systems innovation of coordinated MDT care between primary and tertiary care, we demonstrated a significant improvement in amputation-free survival, metabolic control, and direct healthcare cost savings. Digital health adjunct *via* a patient-owned wound surveillance system may be helpful within this ecosystem.

PhD-related Grants, Presentations, Awards, and Media Releases

Scientific grants awarded during PhD period (2020–2023):

- 2020: Principle Investigator "Lower Extremity Amputation Prevention Program (LEAPP) Collaboration"
    - Collaboration with A*STAR Skin Research Institute of Singapore with funding of S$138,000 to Tan Tock Seng Hospital (H17/01/a/0/0PP9)
- 2020: Principle Investigator "Diabetic Foot in Primary and Tertiary (DEFINITE) Care"
    - Collaboration with Khoo Teck Puat Hospital, NHG Polyclinics with funding of S$2,191,865 by FY2020 NHG Population Health Grant (PHG20/S/X/1/1)
- 2020: Principle Investigator "Pilot study on efficacy of patient-owned wound surveillance system for diabetic foot ulcer care (ePOWS)"
    - Skin Innovation Grant with $100,000 funding from eKare and matched S$100,000 funding from Skin Research Institute of Singapore (SIG2002), a collaboration between TTSH, KTPH, NHGP, SRIS, NTU-LKC and eKare
- 2021: Principle Investigator "Evaluating and Decreasing the Socio-Economical Burden of Wound Care in Singapore through Health Systems Innovations and Health Literacy"
    - National Research Medical Council (NMRC) Research Training Fellowship (RTF) award of S$500,000 (FLWSHP19nov-0015; MOH-000764-00)
- 2021: Principle Investigator "Clinical Validation of Artificial Intelligence Image Analysis on Asian Wound Images"
    - Collaboration with AITI Solutions (spin-off from Delta Capita Limited) with S$66,120 funding to Woodlands Health
- 2022: Principle Investigator "Patient Reported Experience Measures in patients with Diabetic Foot Ulcers"
    - Woodlands Health Small Projects Utilizing Teams (SPROUTS) grant S$10,000 (SPR3-22-CII-01)
- 2023: Principle Investigator "Developing a Smartphone-based Automated Diabetic Foot Screening Solution (Project eDFS)
    - CMTi Medtech Grant award of $50,000 (CMTi-23-01-01)

Scientific presentations/invited speakerships during PhD period (2020–2023):

- 2020: International Society for Pharmaco-economics and Outcomes Research (Europe (Virtual)
    - Clinical and Economic Burden of Diabetic Foot Ulcers: A 5-Year Longitudinal Institutional Population Health Review
- 2020: 4th Wound Care in Tropics Forum (Singapore)
    - DEFINITE WiCC-ed LEAPP in Wound Care at NHG
- 2021: 2nd International Conference on Wound Care, Tissue Repair and Regenerative Medicine (online)
    - Clinical and economic burden of diabetic foot ulcers
- 2021: Singapore Health and Biomedical Congress 2021 (Singapore)
    - Track 4C: Metabolic Health & Diabetic Management – Diabetic Foot in Primary and Tertiary (DEFINITE) Care
- 2022: International Diabetic Foot Symposium (Saudi Arabia)
    - Clinical and economic burden of diabetic foot ulcers: A 5-year longitudinal multiethnic cohort study from the tropics
- 2022: Moderator at Society of Vascular and Endovascular Surgeons of Singapore Journal Club
    - Time is Tissue: Reducing complications and maximizing outcomes for DFU patients
- 2022: 44th Charing Cross Symposium (London, United Kingdom)
    - DEFINITE Care: 1-year results from an interinstitutional and multidisciplinary team health systems innovation at a healthcare cluster from the Tropics
    - Using artificial intelligence to develop a predictive model for risk of amputations in patients with diabetic foot disease
- 2022: Vascular Annual Meeting (Boston, United States of America)
    - Awarded traveling fellowship as ***International Scholars' Program***
    - Visited Massachusetts General Hospital (Boston), University of Southern California Keck School of Medicine (Los Angeles), NYU Langone School of Medicine (New York)
- 2022: Singapore Skin Research Webinar Series
    - Health services approach to the care of diabetic foot ulcers: a DEFINITE LEAPP forward

- 2022: Diabetic Foot Conference 2022 (Los Angeles, United States of America)
    - Diabetic Foot in Primary and Tertiary (DEFINITE) Care: an interinstitutional and multidisciplinary team health systems innovation
    - ***Best Paper Award***
- 2022: Ministry of Health (MOH) Healthier SG Care Protocols Workgroup (Singapore)
    - National Healthcare Group sharing on DEFINITE Care
- 2022: MICCAI 2022 Diabetic Foot Ulcer Challenge 2022 (Singapore)
    - Keynote Speaker: "Wound Imaging Solutions – Where are we in 2022"
- 2022: A*STAR Skin Research Institute of Singapore Wound Care Innovations in the Tropics Forum 2022 (Singapore)
    - DEFINITE Care for patients with diabetic foot ulcers within NHG
- 2022: Woodlands Health INSPIRE Congress: Holistic Management of Diabetic Foot Disease @ Woodlands Health
    - NHG DEFINITE Program – latest updates
- 2022: Faculty and Speaker for Complex Wound Management Masterclass (Bangkok, Thailand)
    - Health Economics of Diabetic Limb Salvage
- 2023: 1st Summit on Management of Diabetic Foot Ulcer (Taiwan, Singapore, Malaysia) (Taipei, Taiwan)
    - Health Systems Innovation in Diabetic Foot Care
- 2023: Economic Impact of Health Services (Saudi Arabia)
    - Health Economics of Diabetic Limb Salvage
- 2023: 45th Charing Cross Symposium (London, United Kingdom)
    - A systematic review and classification of factors influencing diabetic foot ulcer treatment adherence, in accordance with the WHO dimensions of adherence to long-term therapies
- 2023: 9th International Symposium on the Diabetic Foot (Hague, Netherlands)
    - Clinical and Economic Outcomes in Diabetic Foot Ulcer Care Re-organization: 18-month Results from an Observational Population Health Cohort Study
    - Patients, carers and healthcare providers' perspectives on a patient-owned surveillance system for diabetic foot ulcer care: A Qualitative Study

- 2023: 7th International Conference of CAHOCON (Consortium of Accredited Healthcare Organizations) (Hyderabad, India)
    - Advances in Wound Care Management
- 2023 : Woodlands Health Office of Research Development and Scholarship (WORDS) Lunchtime Seminar (Singapore)
    - 101 of Grant Writing and Management
- 2023: Woodlands Health Hospital Seminar (Singapore)
    - Putting Our Best Foot Forward – Diabetic Foot Program at WH
- 2023 : Molnlycke Asia-Pacific Chronic Wound Summit (Bangkok, Thailand)
    - M.O.I.S.T. focus group discussion
- 2023 : St Luke's Elder Care Wound Symposium (Singapore)
    - Healing the Hole in Diabetic Foot Ulcers Requires Holistic Care for the Whole Patient
- 2023 : Moderator at Podiatry Association of Singapore Dinner Symposium (Singapore)
    - Paradigm shift in the use of antimicrobial wound dressing technology
- 2024 : The Biofilm Matrix: Fundamental Understanding and Translational Impact (Singapore)
    - Biofilm Matrix: Translational Impact in Chronic Wounds
- 2024 : 32nd Philippine Orthopedic Association Midyear Convention – Advanced Wound Care in the New Normal (Palawan, Philippines)
    - Holistic Care of the Whole Patient with the Diabetic Foot Hole
    - Establishing wound care and research services for a new 1,800 bed hospital in Singapore

Awards/prizes received during PhD period (2020-2023):

- 2020 : Awarded Society of Vascular Surgery International Scholars Program
- 2021 : Awarded National Research Medical Council (NMRC) Research Training Fellowship (RTF)
- 2021 : SG Healthcare AI Datathon 2nd runner-up (in collaboration with AITIS)
- 2022 : Wiley Top Cited Article 2020-2021 in International Wound Journal – Clinical and economic burden of wound care in the tropics: a 5-year institutional population health review
- 2022 : Wiley Top Downloaded Article 2021 in International Wound Journal – Clinical and economic burden of diabetic foot ulcers: A 5-year longitudinal multi-ethnic cohort study from the tropics
- 2022 : Diabetic Foot Conference (DFCon) 2022 Best Paper Award (Los Angeles, USA)
- 2022 : NUS-YLL School of Medicine Dean's Award for Teaching Excellence 2021/2022
- 2022 : NHG Quality Improvement Award (Innovation in Healthcare) Merit Award
- 2022 : Singapore National Healthcare Innovation and Productivity Medal (Care Redesign)
- 2023 : Wiley Top Cited Article 2021-2022 in International Wound Journal – Clinical and economic burden of wound care in the tropics: a 5-year institutional population health review
- 2023 : National Healthcare Group Teaching Award for Senior Doctors
- 2023 : National Awards (Singapore): COVID-19 Resilience Medal

Media Coverage during PhD period (2020-2023):

- 2020 : iWounds News – Five-year review of Singapore primary care system demonstrates rising impact of chronic wounds
    - https://iwoundsnews.com/five-year-review-singapore-rising-impact-chronic-wounds/ (20 Mar 2020)
- 2020 : National Healthcare Group e-CATALYST (Nov-Dec 2020) – Clinical Validation and Improvement of WoundAide Imaging System
    - https://www.research.nhg.com.sg/wps/wcm/connect/49652d0040f223fb8780f70c9e9c42b6/eCatalyst_42.pdf?MOD=AJPERES
- 2021 : DEFINITE Care Program
    - Broadcast: Channel News Asia, Channel 8, Channel U, Radio Capital 95.8FM, Radio CNA938
    - Rate of amputation drastically reduced for more than 2,700 patients with diabetes who participated in the foot care programme (1 Oct 2021) https://www.zaobao.com.sg/news/singapore/story20211002-1199251
    - NHG launches new program to reduce diabetes-related amputations (1 Oct 2021) https://www.8world.com/singapore/nhg-diabetes-foot-care-1605371
    - NHG programme for diabetic foot disease reduces major amputations by 40 per cent (7 Oct 2021) https://www.straitstimes.com/singapore/health/nhg-programme-for-diabetic-foot-disease-reduces-major-amputations-by-40-per-cent
    - 40 per cent reduction in amputation cases for patients with diabetes (7 Oct 2021) https://www.beritaharian.sg/setempat/kes-amputasi-bagi-pesakit-kencing-manis-kurang-40
- 2020/2021 NHG Corporate Yearbook : Population Health
    - Putting a "DEFINITE" Foot Forward https://corp.nhg.com.sg/Documents/CYB%202021%20Digital/population-health.html
- 2022 : Issue 2 Jan 2022 LKCMedicine STRIDES
    - Graduate Students News: SG Healthcare AI Datathon 2021 Award https://ebook.ntu.edu.sg/lkcmedicine-strides_jan2022.html

- 2022 : Charing Cross Symposium Daily News 18 April 2022
    - Researchers develop predictive model for risk of amputation in diabetic foot patients
- 2022 : National Healthcare Group e-CATALYST (May-Jun 2022)
    - Not a Marathon and Not a Hackathon, but a Datathon!
    - NHG Wounds iCare Collaborative (WiCC) Research and Clinical Workgroup
    - Singapore Wound Registry – A Collaboration Between Skin Research Institute of Singapore, SingHealth, National University Health System and National Healthcare Group
      https://www.research.nhg.com.sg/wps/wcm/connect/df6a0113-27a5-4e14-8b6d-c9c34dc9ff9c/eCatalyst+Issue+45+Newsletter.pdf?MOD=AJPERES&CVID=o3lP3mE&CVID=o3lP3mE&CVID=o3lP3mE&CVID=o3lP3mE&CVID=o3lP3mE
- 2023 : Woodlands Health Yearbook 2022/2023
    - Honing our delivery of care – INSPIRE Congress 2022: Holistic Management od Diabetic Foot Disease @ Woodlands Health
    - Driving Innovation and Research
      https://www.wh.com.sg/AboutUs/Documents/WH_Corp_Yearbook_FY22.pdf
- 2023 : WORDS Newsletter Issue 1, June 2023
    - Spotlight on Clinician-Scientist
      https://www.dropbox.com/scl/fi/hooqz7g5yzm3mvovaft77/ForWORDS-Newsletter_June-2023.pdf?rlkey=prgt7mrgttlanhcot7sv2v7fg&dl=0
- 2023 : Diabetic Foot Online
    - Embracing Home Digital Surveillance: A Step Forward in DFU Care?
      https://diabeticfootonline.com/2023/10/15/embracing-home-digital-surveillance-a-step-forward-in-diabetic-foot-ulcer-care/
- 2024 : Diabetic Foot Online
    - David G Armstrong Honored as Distinguished Visiting Professor in Singapore for Limb Preservation
      https://diabeticfootonline.com/2024/02/02/david-g-armstrong-honored-as-distinguished-visiting-professor-in-singapore-for-limb-preservation-actagainstamputation/

- 2024 : Diabetic Foot Online
    - A Closer Look at DFU Treatment Adherence using WHO criteria https://diabeticfootonline.com/2024/02/07/a-closer-look-at-diabetic-foot-ulcer-treatment-adherence-using-who-criteria-ijlew-actagainstamputation-diabeticfoot/

References

1. International Diabetes Federation. IDF Diabetes Atlas, 10th ed. Brussels, Belgium: 2021. Available at https://www.diabetesatlas.org. Assessed 1 Aug 2023.
2. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017; 376: 2367-2375.
3. Armstrong DG, TW Tan, AJM Boulton, SA Bus. Diabetic Foot Ulcers: A Review. JAMA 2023: 330(1):62-75
4. Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global disability burdens of diabetes-related lower-extremity complications in 1990 and 2016. Diabetes Care 2020; 43: 964-974.
5. Amin N, Doupis J. Diabetic foot disease: from the evaluation of the "foot at risk" to the novel diabetic ulcer treatment modalities. World J Diabetes 2016; 7: 153-164.
6. Prompers L, Huijberts M, Apelqvist J, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia 2007; 50: 18-25.
7. Senneville É, Albalawi Z, van Asten SA, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes: IWGDF/IDSA 2023. Published 2023. Available at https://iwgdfguidelines.org/wp-content/uploads/2023/05/IWGDF-2023-04-Infection-Guideline.pdf. Assessed 1 Aug 2023.
8. Skrepnek GH, Mills JL Sr, Armstrong DG. A diabetic emergency one million feet long: disparities and burdens of illness among diabetic foot ulcer cases within emergency departments in the United States, 2006–2010. PLOS ONE 2015; 10: e0134914.
9. Skrepnek GH, Mills JL Sr, Lavery LA, Armstrong DG. Health care service and outcomes among an estimated 6.7 million ambulatory care diabetic foot cases in the U.S. Diabetes Care 2017; 40: 936-942.
10. Kerr M, Rayman G, Jeffcoate WJ. Cost of diabetic foot disease to the national health service in England. Diabet Med 2014; 31: 1498-1504.
11. Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global disability burdens of diabetes-related lower-extremity complications in 1990 and 2016. Diabetes Care 2020; 43: 964-974.

12. Narres M, Kvitkina T, Claessen H, et al. Incidence of lower extremity amputations in the diabetic compared with the non-diabetic population: a systematic review. PLOS ONE 2017; 12: e0182081.
13. McDermott K, Fang M, Boulton AJM, Selvin E, Hicks CW. Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers. Diabetes Care 2023; 46: 209-221.
14. Behrendt CA, Sigvant B, Szeberin Z, et al. International variations in amputation practice: a VASCUNET report. Eur J Vasc Endovasc Surg 2018; 56: 391-399.
15. Walsh JW, Hoffstad OJ, Sullivan MO, Margolis DJ. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. Diabet Med 2016; 33: 1493-1498.
16. Saluja S, Anderson SG, Hambleton I, et al. Foot ulceration and its association with mortality in diabetes mellitus: a meta-analysis. Diabet Med 2020; 37: 211-218.
17. Armstrong DG, Swerdlow MA, Armstrong AA, Conte MS, Padula WV, Bus SA. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. J Foot Ankle Res 2020; 13: 16.
18. Lavery LA, Hunt NA, Ndip A, Lavery DC, Van Houtum W, Boulton AJ. Impact of chronic kidney disease on survival after amputation in individuals with diabetes. Diabetes Care 2010; 33: 2365-2369.
19. Iversen MM, Tell GS, Riise T, et al. History of foot ulcer increases mortality among individuals with diabetes: ten-year follow-up of the Nord-Trøndelag health study, Norway. Diabetes Care 2009; 32: 2193-2199.
20. Petersen BJ, Linde-Zwirble WT, Tan TW, et al. Higher rates of all-cause mortality and resource utilization during episodes-of-care for diabetic foot ulceration. Diabetes Res Clin Pract 2022; 184: 109182.
21. Jiang FH, Liu XM, Yu HR, Qian Y, Chen HL. The incidence of depression in patients with diabetic foot ulcers: a systematic review and meta-analysis. Int J Low Extrem Wounds 2022; 21: 161-173.
22. Siersma V, Thorsen H, Holstein PE, et al. Importance of factors determining the low health-related quality of life in people presenting with a diabetic foot ulcer: the Eurodiale study. Diabet Med 2013; 30: 1382-1387.
23. Hogg FRA, Peach G, Price P, Thompson MM, Hinchliffe RJ. Measures of health-related quality of life in diabetes-related foot disease: a systematic review. Diabetologia 2012; 55: 552-565.

24. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013; 36: 1033-1046.
25. Rice JB, Desai U, Cummings AKG, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for Medicare and private insurers. Diabetes Care 2014; 37: 651-658.
26. Kerr M, Barron E, Chadwick P, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabet Med 2019; 36: 995-1002.
27. Petrakis I, Kyriopoulos IJ, Ginis A, Athanasakis K. Losing a foot versus losing a dollar; a systematic review of cost studies in diabetic foot complications. Expert Rev Pharmacoecon Outcomes Res 2017; 17: 165-180.
28. Tchero H, Kangambega P, Lin L, et al. Cost of diabetic foot in France, Spain, Italy, Germany and United Kingdom: a systematic review. Ann Endocrinol (Paris) 2018; 79: 67-74.
29. Armstrong DG, Mills JL. Toward a change in syntax in diabetic foot care: prevention equals remission. J Am Podiatr Med Assoc 2013; 103: 161-162.
30. International Working Group for Diabetic Foot Guidelines 2023. Available at https://iwgdfguidelines.org/guidelines-2023/ Accessed 1 Aug 2023
31. Monteiro-Soares M, Vale-Lima J, Martiniano J, Pinheiro-Torres S, Dias V, Boyko EJ. A systematic review with meta-analysis of the impact of access and quality of diabetic foot care delivery in preventing lower extremity amputation. J Diabetes Complications 2021; 35: 107837.
32. Musuuza J, Sutherland BL, Kurter S, Balasubramanian P, Bartels CM, Brennan MB. A systematic review of multidisciplinary teams to reduce major amputations for patients with diabetic foot ulcers. J Vasc Surg 2020; 71: 1433-1446.e3.
33. Edmonds M, Manu C, Vas P. The current burden of diabetic foot disease. J Clin Orthop Trauma 2021; 17: 88-93.
34. Luo B, Cai Y, Chen D, et al. Effects of special therapeutic footwear on the prevention of diabetic foot ulcers: a systematic review and meta-analysis of randomized controlled trials. J Diabetes Res 2022; 2022: 9742665.
35. van Netten JJ, Raspovic A, Lavery LA et al.. Prevention of foot ulcers in persons with diabetes at risk of ulceration: a systematic review and meta-analysis. Diabetes Metabolism Res. 2023. doi: 10.1002/dmrr.3652
36. Driver VR, Fabbi M, Lavery LA, Gibbons G. The costs of diabetic foot: the economic case for the limb salvage team. J Vasc Surg 2010; 52: 17S-22S.

37. Phan TP, Alkema L, Tai ES, et al. Forecasting the burden of type 2 diabetes in Singapore using a demographic epidemiological model of Singapore. BMJ Open Diabetes Res Care 2014; 2: e000012.
38. Ang Y, Yap CW, Saxena N, Lin L, Heng BH. Diabetes-related lower extremity amputations in Singapore. Proc Singapore Healthc 2017; 26: 76-80.
39. Carinci F, Uccioli L, Massi Benedetti MM, Klazinga NS. An in-depth assessment of diabetes-related lower extremity amputation rates 2000-2013 delivered by twenty-one countries for the data collection 2015 of the Organization for Economic Cooperation and Development (OECD). Acta Diabetol 2020; 57: 347-357.
40. Ow Yong LM, Koe LWP. War on diabetes in Singapore: a policy analysis. Health Res Policy Syst 2021; 19: 15.
41. Ministry of Health – Singapore, Singapore's Healthcare System. 2020. Available at https://moh.gov.sg/home/our-healthcare-system Accessed 1 Aug 2023
42. National Healthcare Group Corporate Yearbook FY2021. Available at https://corp.nhg.com.sg/Lists/Corporate%20Year%20Book/Attachments/71/NHG%20Yearbook%202021%20Lowres%20Single.pdf Accessed 1 Aug 2023
43. Singapore Government. Singapore Residents by Age Group, Ethnic Group and Gender. Available at https://data.gov.sg/dataset/resident-population-by-ethnicity-gender-and-age-group Accessed 1 Aug 2023.
44. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011; 173: 676-682.
45. Cuschieri S. The STROBE guidelines. Saudi J Anaesth 2019; 13: S31-S34.
46. Agency for Care Effectiveness. Appropriate Care Guide: Foot Assessment in People with Diabetes. Available at https://www.ace-hta.gov.sg/public-data/our-guidance/Foot%20assessment%20in%20people%20with%20diabetes%20(June%202019).pdf Accessed Aug 20, 2020.
47. National Institute for Health and Care Excellence Clinical Guideline CG147. Peripheral Arterial Disease: Diagnosis and Management. 2018. Available at https://www.nice.org.uk/guidance/cg147 Accessed 1 Aug 2023
48. Zielinski M, Paola LD, Martinez JLL. A multidisciplinary approach for the management of diabetic foot ulcers. Wounds Int 2018; 9: 44-49.

49. Joret MO, Osman K, Dean A, Cao C, van der Werf B, Bhamidipaty V. Multidisciplinary clinics reduce treatment costs and improve patient outcomes in diabetic foot disease. J Vasc Surg 2019; 70: 806-814.
50. Buggy A, Moore Z. The impact of the multidisciplinary team in the management of individuals with diabetic foot ulcers: a systematic review. J Wound Care 2017; 26: 324-339.
51. Khan T, Shin L, Woelfel S, Rowe V, Wilson BL, Armstrong DG. Building a scalable diabetic limb preservation program: four steps to success. Diabet Foot Ankle 2018; 9: 1452513.
52. Fitzgerald RH, Mills JL, Joseph W, Armstrong DG. The diabetic rapid response acute foot team: 7 essential skills for targeted limb salvage. EPlasty 2009; 9: e15.
53. National Healthcare Innovation and Productivity Medal (Care Redesign) 2022. Available at https://youtu.be/0y7M_8a_7CI?si=tmy4558nA4V9NYK4&t=71 Accessed 1 Aug 2023
54. Janssen M, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Quality of life research 2013;22:1717-27.
55. Abetz L, Sutton M, Brady L, et al. The Diabetic Foot Ulcer Scale (DFS): a quality of life instrument for use in clinical trials. Practical Diabetes International 2002;19:167-75.
56. Standardization IOF. Ergonomics of Human-System Interaction. Human-Centred Design for Interactive Systems (ISO 9241-210:2019) 2019. Available at https://www.iso.org/standard/77520.html Assessed 1 Aug 2023.
57. Swerdlow M, Lo J, Armstrong DG. Reliability of an AI-powered application across different mobile devices for assessment of chronic wounds. Adv Wound Care 2023.
58. Lasschuit JWJ, Featherston J, Tonks KTT. Reliability of a three-dimensional wound camera and correlation with routine ruler measurement in diabetes-related foot ulceration. J Diabetes Sci Technol 2021; 15: 1361-1367.
59. Lo ZJ, Chong B, Tan E, et al. Patients, carers and healthcare providers' perspectives on a patient-owned surveillance system for diabetic foot ulcer care: a qualitative study. Digit Health 2023; 9: 20552076231183544.
60. Riandini T, Pang D, Toh MPHS, et al. National rates of lower extremity amputation in people with and without diabetes in a multi-ethnic Asian population: a ten year study in Singapore. Eur J Vasc Endovasc Surg 2022; 63: 147-155.
61. Wu H, Yang A, Lau ESH, Ma RCW, Kong APS, Chow E, So WY, Chan JCN, Luk AOY. Secular trends in rates of hospitalisation for lower extremity amputation and 1 year

mortality in people with diabetes in Hong Kong, 2001-2016: a retrospective cohort study. Diabetologia. 2020; 63:2689-2698

62. Roikjer J, Jensen MH, Vestergaard P, Sorensen AM, Laursen HVB, Ejskjaer. Twenty years with diabetes and amputations: a retrospective population-based cohort study. Diabet Med 2020; 37:2098-2108
63. Lo ZJ, Lim X, Eng D, et al. Clinical and economic burden of wound care in the tropics: a 5-year institutional population health review. Int Wound J 2020; 17: 790-803.
64. Faglia E, Dalla Paola L, Clerici G, et al. Peripheral angioplasty as the first-choice revascularization procedure in diabetic patients with critical limb ischemia: prospective study of 993 consecutive patients hospitalized and followed between 1999 and 2003. Eur J Vasc Endovasc Surg 2005; 29: 620-627.
65. Dubský M, Jirkovská A, Bem R, et al. Risk factors for recurrence of diabetic foot ulcers: prospective follow-up analysis in the Eurodiale subgroup. Int Wound J 2013; 10: 555-561.
66. Parisi MCR, Moura Neto A, Menezes FH, et al. Baseline characteristics and risk factors for ulcer, amputation and severe neuropathy in diabetic foot at risk: the BRAZUPA study. Diabetol Metab Syndr 2016; 8: 25.
67. Banik PC, Barua L, Moniruzzaman M, Mondal R, Zaman F, Ali L. Risk of diabetic foot ulcer and its associated factors among Bangladeshi subjects: a multicentric cross-sectional study. BMJ Open 2020; 10: e034058.
68. Siddiqui MA, Khan MF, Carline TE. Gender differences in living with diabetes mellitus. Mater Sociomed 2013; 25: 140-142.
69. Nather A, Bee CS, Huak CY et al.. Epidemiology of diabetic foot problems and predictive factors for limb loss. J Diabetes Complications 2008; 22: 77-82.
70. Lo ZJ, Lin Z, Pua U, et al. Diabetic foot limb salvage-A series of 809 attempts and predictors for endovascular limb salvage failure. Ann Vasc Surg 2018; 49: 9-16.
71. Yong E, Gong H, Liew H, et al. Getting a foothold on diabetic foot disease – outcomes of a multidisciplinary clinical pathway for inpatient diabetic foot care: a 17-year institutional review. Int J Low Extremity Wounds 2023 27 Jun.
72. Riandini T, Pang D, Toh MPHS, et al. National rates of lower extremity amputation in people with and without diabetes in a multi-ethnic Asian population: a ten year study in Singapore. Eur J Vasc Endovasc Surg 2022; 63: 147-155.
73. Young BA, Lin E, Von Korff M, et al. Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. Am J Manag Care 2008; 14: 15-23.

74. Zhou ZY, Liu YK, Chen HL, Yang HL, Liu F. HbA1c and lower extremity amputation risk in patients with diabetes: a meta-analysis. Int J Low Extrem Wounds 2015; 14: 168-177.
75. Christman AL, Selvin E, Margolis DJ, Lazarus GS, Garza LA. Hemoglobin A1c predicts healing rate in diabetic wounds. J Invest Dermatol 2011; 131: 2121-2127.
76. Lane KL, Abusamaan MS, Voss BF, et al. Glycemic control and diabetic foot ulcer outcomes: a systematic review and meta-analysis of observational studies. J Diabetes Complications 2020; 34: 107638.
77. Moulik PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. Diabetes Care 2003; 26: 491-494.
78. Amadou C, Carlier A, Amouyal C, et al. Five-year mortality in patients with diabetic foot ulcer during 2009-2010 was lower than expected. Diabetes Metab 2020; 46: 230-235.
79. Ministry of Health – Singapore. Prevalence of diabetes in Singapore. Available at https://data.gov.sg/dataset/prevalence-of-hypertension-diabetes-high-total-cholesterol-obesity-and-daily-smoking Assessed 1 Aug 2023.
80. Png ME, Yoong J, Phan TP, Wee HL. Current and future economic burden of diabetes among working-age adults in Asia: conservative estimates for Singapore from 2010-2050. BMC Public Health 2016; 16: 153.
81. Ragnarson Tennvall G, Apelqvist J. Health-economic consequences of diabetic foot lesions. Clin Infect Dis 2004; 39: S132-S139.
82. Ortegon MM, Redekop WK, Niessen LW. Cost-effectiveness of prevention and treatment of the diabetic foot: a Markov analysis. Diabetes Care 2004; 27: 901-907.
83. Krishnan S, Nash F, Baker N, Fowler D, Rayman G. Reduction in diabetic amputations over 11 years in a defined U.K. population: benefits of multidisciplinary team work and continuous prospective audit. Diabetes Care 2008; 31: 99-101.
84. Almdal T, Nielsen AA, Nielsen KE, et al. Increased healing in diabetic toe ulcers in a multidisciplinary foot clinic-an observational cohort study. Diabetes Res Clin Pract 2015; 110: 315-321.
85. Wang C, Mai L, Yang C, et al. Reducing major lower extremity amputations after the introduction of a multidisciplinary team in patient with diabetes foot ulcer. BMC Endocr Disord 2016; 16: 38.
86. Huang DY, Wilkins CJ, Evans DR, et al. The diabetic foot: the importance of coordinated care. Semin Intervent Radiol 2014; 31: 307-312.

87. Zayed H, Halawa M, Maillardet L, Sidhu PS, Edmonds M, Rashid H. Improving limb salvage rate in diabetic patients with critical leg ischaemia using a multidisciplinary approach. Int J Clin Pract 2009; 63: 855-858.
88. Kim PJ, Attinger CE, Steinberg JS, et al. Building a multidisciplinary hospital-based wound care center: nuts and bolts. Plast Reconstr Surg 2016; 138: 241S-247S.
89. Nather A, Siok Bee C, Keng Lin W, et al. Value of team approach combined with clinical pathway for diabetic foot problems: a clinical evaluation. Diabet Foot Ankle 2010; 1: 5731.
90. Tan MLM, Feng J, Gordois A, Wong ESD. Lower extremity amputation prevention in Singapore: economic analysis of results. Singapore Med J 2011; 52: 662-668.
91. Ellner AL, Stout S, Sullivan EE, et al. Health Systems Innovation at Academic Health Centers. Academic Medicine. 2015; 90(7):872-880
92. Fox A, Gardner G, Osborne S. A theoretical framework to support research of health service innovation. Aust Health Rev 2015; 39: 70-75.
93. Blanchette V, Brousseau-Foley M, Cloutier L. Effect of contact with podiatry in a team approach context on diabetic foot ulcer and lower extremity amputation: systematic review and meta-analysis. J Foot Ankle Res 2020; 13: 15.
94. Crawford F, Nicolson DJ, Amanna AE, et al. Preventing foot ulceration in diabetes: systematic review and meta-analyses of RCT data. Diabetologia 2020; 63: 49-64.
95. Riandini T, Pang D, Toh MPHS, et al. Diabetes-related lower extremity complications in a multi-ethnic Asian population: a 10 year observational study in Singapore. Diabetologia 2021; 64: 1538-1549.
96. Iida O, Nakamura M, Yamauchi Y et al. 3-year outcomes of the olive registry, a prospective multicenter study of patients with critical limb ischemia: a prospective, multi-center, three-year follow-up study on endovascular treatment for infra-inguinal vessel in patients with critical limb ischemia. JACC Cardiovasc Interv 2015; 8: 1493-1502.
97. Li X, Xiao T, Wang Y, et al. Incidence, risk factors for amputation among patients with diabetic foot ulcer in a Chinese tertiary hospital. Diabetes Res Clin Pract 2011; 93: 26-30.
98. Brownrigg JR, Davey J, Holt PJ, et al. The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: a meta-analysis. Diabetologia 2012; 55: 2906-2912.
99. Rubio JA, Jiménez S, Lázaro-Martínez JL. Mortality in patients with diabetic foot ulcers: causes, risk factors, and their association with evolution and severity of ulcer. J Clin Med 2020; 9: 3009.

100. Tennvall GR, Apelqvist J. Health-economic consequences of diabetic foot lesions. Clin Infect Dis. 2004; 39(2): S132-S139.

101. Ollendorf DA, Kotsanos JG, Wishner WJ, et al. Potential economic benefits of lower-extremity amputation prevention. Diabetes Care. 1998; 21(8): 1240-1245.

102. Nabuurs-Franssen MH, Huijberts M, Nieuwenhuijzen Kruseman A, et al. Health-related quality of life of diabetic foot ulcer patients and their caregivers. Diabetologia 2005;48:1906-10.

103. Gorecki C, Brown JM, Nelson EA, et al. Impact of pressure ulcers on quality of life in older patients: a systematic review. Journal of the American Geriatrics Society 2009;57:1175-83.

104. Herber OR, Schnepp W, Rieger MA. A systematic review on the impact of leg ulceration on patients' quality of life. Health and quality of life outcomes 2007;5:1-12.

105. Ang GY, Yap CW, Saxena N. Effectiveness of diabetes foot screening in primary care in preventing lower extremity amputations. Ann Acad Med Singapore 2017; 46: 417-423.

106. World health O. Adherence to long-term therapies: evidence for action. In. Geneva: World Health Organization; 2003.

107. GWY Ng, KF Gan, H Liew, L Ge, G Ang, J Molina, Y Sun, PS Prakash, KB Harish, ZJ Lo. A Systematic Review and Classification of Factors Influencing Diabetic Foot Ulcer Treatment Adherence, in Accordance with the WHO Dimensions of Adherence to Long-Term Therapies. Int J of Lower Extremity Wounds. 2024. Doi:10.1177/15347346241233962

108. Wilkinson J, Daly M. Reasons for non-attendance: audit findings from a nurse-led clinic. J Prim Health Care. 2012;4(1):39-44.

109. Fayfman M, Schechter MC, Amobi CN, et al. Barriers to diabetic foot care in a disadvantaged population: A qualitative assessment. Journal of Diabetes and its Complications. 2020;34(12):107688. doi:10.1016/j.jdiacomp.2020.107688

110. Dehdari L, Dehdari T. The determinants of anti-diabetic medication adherence based on the experiences of patients with type 2 diabetes. Archives of Public Health. 2019;77(1):21. doi:10.1186/s13690-019-0347

111. Pourhabibi N, Mohebbi B, Sadeghi R, et al. Factors associated with treatment adherence to treatment among in patients with type 2 diabetes in Iran: A cross-sectional study. Front Public Health. 2022;10:976888. doi:10.3389/fpubh.2022.976888

112. Suzuki R, Saita S, Nishigaki N, et al. Factors associated with treatment adherence and satisfaction in type 2 diabetes management in Japan: Results from a web-based

questionnaire survey. Diabetes Ther. 2021;12(9):2343-2358. doi:10.1007/s13300-021-01100-3

113. Parker MM, Moffet HH, Schillinger D, et al. Ethnic differences in appointment-keeping and implications for the patient-centered medical home--findings from the Diabetes Study of Northern California (DISTANCE). Health Serv Res. 2012;47(2):572-593. doi:10.1111/j.1475-6773.2011.01337

114. Peng X, Gou D, Zhang L, et al. Status and influencing factors of lower limb amputation in patients with diabetic foot ulcer. Int Wound J. 2023;20(6):2075-2081. doi:10.1111/iwj.14076

115. Selby JV, Zhang D. Risk factors for lower extremity amputation in persons with diabetes. Diabetes Care. 1995;18(4):509-516. doi:10.2337/diacare.18.4.509

116. Armstrong DG, Harkless LB. Outcomes of preventative care in a diabetic foot specialty clinic. The Journal of Foot and Ankle Surgery. 1998;37(6):460-466. doi:10.1016/S1067-2516(98)80022-7

117. Primadhi RA, Septrina R, Hapsari P, Kusumawati M. Amputation in diabetic foot ulcer: a treatment dilemma. World J Orthop. 2023;14(5):312-318.

118. Morbach S, Furchert H, Gröblinghoff U, et al. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. Diabetes Care. 2012;35(10): 2021-2027.

119. Aragon-Sanchez J, Víquez-Molina G, Lopez-Valverde ME, Aragon-Hernandez C, Aragon-Hernandez J, Rojas-Bonilla JM. Clinical features, inflammatory markers, and limb salvage in older adults with diabetes-related foot infections. Int J Low Extrem Wounds. 2023; 15347346231154472. doi:10.1177/15347346231154472

120. Dosluoglu HH, Lall P, Cherr GS, Harris LM, Dryjski ML. Superior limb salvage with endovascular therapy in octogenarians with critical limb ischemia. J Vasc Surg. 2009;50(2):305-316.e2.

121. Choi MSS, Jeon SB, Lee JH. Predictive factors for successful limb salvage surgery in diabetic foot patients. BMC Surg. 2014; 14(1):113.

122. Wang C, Mai L, Yang C, et al. Reducing major lower extremity amputations after the introduction of a multidisciplinary team in patient with diabetes foot ulcer. BMC Endocr Disord. 2016;16:38.

123. Almdal T, Nielsen AA, Nielsen KE, et al. Increased healing in diabetic toe ulcers in a multidisciplinary foot clinic - an observational cohort study. Diabetes Res Clin Pract. 2015;110(3):315-321.

124. Natesan S, Li JY, Kyaw KK, et al. Effectiveness of comanagement model: geriatric medicine and vascular surgery. J Am Med Dir Assoc. 2022;23(4):666-670.
125. Tan TW, Shih CD, Concha-Moore KC, Diri MM, Hu B, Marrero D, Zhou W, Armstrong DG. Disparities in outcomes of patients admitted with diabetic foot infections. PLOS ONE. 2019; 14(2):e0211481
126. Chan CQH, Lee KH, Low LL. A systematic review of health status, health seeking behaviour and healthcare utilisation of low socioeconomic status populations in urban Singapore. Int J Equity Health. 2018; 17:39
127. Nather A, Chionh SB, Lin WK, Koh SQO, Chan YH, Li X, Nambiar A. Socioeconomic profile of diabetic patients with and without foot problems. Diabetic Foot & Ankle. 2010; 1:1
128. Boodoo C, Perry JA, Hunter PJ, et al. Views of patients on using mhealth to monitor and prevent diabetic foot ulcers: qualitative study. JMIR Diabetes 2017; 2: e22.
129. Fischer SH, David D, Crotty BH, Dierks M, Safran C. Acceptance and use of health information technology by community-dwelling elders. Int J Med Inform 2014; 83: 624-635.
130. Davenport RD, Mann W, Lutz B. How older adults make decisions regarding smart technology: an ethnographic approach. Assist Technol 2012; 24: 168-81; quiz 182.
131. Alvarado MM, Kum HC, Gonzalez Coronado K, Foster MJ, Ortega P, Lawley MA. Barriers to remote health interventions for Type 2 diabetes: a systematic review and proposed classification scheme. J Med Internet Res 2017; 19: e28.
132. LeRouge C, Van Slyke C, Seale D, Wright K. Baby boomers' adoption of consumer health technologies: survey on readiness and barriers. J Med Internet Res 2014; 16: e200.
133. Wallace D, Perry J, Yu J, Mehta J, Hunter P, Cross KM. Assessing the need for mobile health (mhealth) in monitoring the diabetic lower extremity. JMIR MHealth UHealth 2019; 7: e11879.
134. Boodoo C, Perry JA, Leung G, Cross KM, Isaranuwatchai W. Cost-effectiveness of telemonitoring screening for diabetic foot ulcer: a mathematical model. CMAJ Open 2018; 6: E486-E494.
135. Tchero H, Noubou L, Becsangele B, Mukisi-Mukaza M, Retali GR, Rusch E. Telemedicine in diabetic foot care: a systematic literature review of interventions and meta-analysis of controlled trials. Int J Low Extrem Wounds 2017; 16: 274-283.

136. Hazenberg CEVB, Aan de Stegge WB, Van Baal SG, Moll FL, Bus SA. Telehealth and telemedicine applications for the diabetic foot: a systematic review. Diabetes Metab Res Rev 2020; 36: e3247.
137. Najafi B, Mishra R. Harnessing digital health technologies to remotely manage diabetic foot syndrome: a narrative review. Medicina (Kaunas) 2021; 57: 377.
138. Keegan AC, Bose S, McDermott KM, et al. Implementation of a patient-centered remote wound monitoring system for management of diabetic foot ulcers. Front Endocrinol 2023. Available at https://www.frontiersin.org/articles/10.3389/fendo.2023.1157518: 1157518. , Accessed Jun 23 2023; 14.
139. Swerdlow M, Shin L, D'Huyvetter K, Mack WJ, Armstrong DG. Initial clinical experience with a simple, home system for early detection and monitoring of diabetic foot ulcers: the foot selfie. J Diabetes Sci Technol 2023; 17: 79-88.
140. Galavi Z, Montazeri M, Ahmadian L. Barriers and challenges of using health information technology in home care: a systematic review. Int J Health Plann Manage 2022; 37: 2542-2568.
141. Ince P, Game FL, Jeffcoate WJ. Rate of healing of neuropathic ulcers of the foot in diabetes and its relationship to ulcer duration and ulcer area. Diabetes Care 2007; 30: 660-663.
142. Zimny S, Pfohl M. Healing times and prediction of wound healing in neuropathic diabetic foot ulcers: a prospective study. Exp Clin Endocrinol Diabetes 2005; 113: 90-93.

Appendix 1: International Classification of Diseases (ICD9 and ICD10) diagnosis, surgical procedure, and service codes utilized for data retrieval,

Categories	ICD9	ICD10	Surgical codes	Service codes
Inpatient discharge primary diagnosis and secondary diagnosis	2507’	E09.0		
	25070’	E09.01		
	25071’	E09.02		
	25072’	E09.5		
	25073’	E09.51		
	4402’	E09.52		
	44020’	E10.51		
	44021’	E10.52		
	44023’	E10.73		
	44024’	E11.51		
	44029’	E11.52		
	4403’	E11.73		
	44030’	E13.51		
	44031’	E13.52		
	44032’	E13.73		
	443’	E14.51		
	4438’	E14.52		
	44389’	E14.73		
	4439’	I70.2		
	4442’	I70.20		
	7854’	I70.21		
		I70.23		
		I70.24		
		I73		
		I73.8		
		I73.9		
		I74.3		
		I74.4		
		I79.2		

Tertiary outpatient wound nurse care				WC001 WC006
Primary care wound visits				NBF017 NHF018 NBF026 NBF030
Angioplasty				SD720A SD721A SD722A XRM019
Surgical bypass				SD713A SD714A SD810V SD814V SD807A
Minor amputations			SB708T SB830T SB707T SB829T	
Major amputations			SB809L	
ABPI Arterial duplex				VS0020 VS0005 VS0006

ABPI: arterial-brachial pressure index

Appendix 2: Memo for patients with healed diabetic foot ulcers.

Discharge Memo regarding Diabetic Foot Surveillance for Healed Diabetic Foot Ulcer (DFU)

Patient Name: ____

Patient NRIC: ____________________

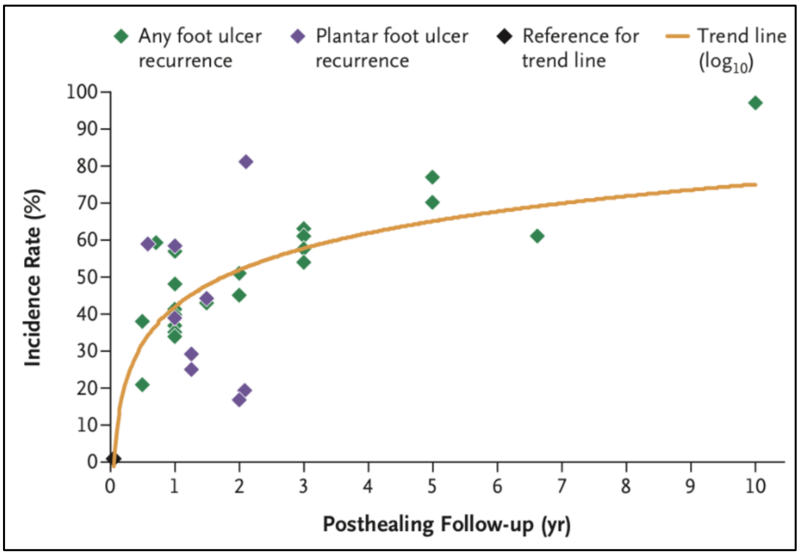
Date: ____________________

Dear colleague,

Thank you for your ongoing care of the above-mentioned patient's diabetic management. He/she has been treated for a **Diabetic Foot Ulcer, which has since healed**.

- ☐ The patient has the following appendices with TTSH/KTPH
  - ☐ Vascular Open TCU (1 year) from ____________ (date)
  - ☐ Podiatry Clinic ____________ (date)
- ☐ The patient does not have any further appointments for his/her DFU.

Your patient is at **high risk of redeveloping DFU**, having just recovered from an episode of DFU. Incidence of ulcer recurrence is around **40% within the first year** (Armstrong, NEJM 2017).



Therefore, to prevent DFU recurrence, your patient requires close monitoring with **3–4 monthly Diabetic Foot Surveillance** and regular patient education to help them care for their feet.

These 3–4 monthly Diabetic Foot Surveillance should include:

1. Examination for skin integrity and deformity of the feet
2. Palpation of pedal pulses and measurement of ankle-brachial pressure index (ABPI) or obtaining absolute systolic toe pressure of each big toe

3. Assessment of foot neuropathy with 10 g monofilament, 128 Hz tuning fork, or neurothesiometer

More details are contained in the **Appropriate Care Guide from MOH on "Foot assessment in people with diabetes,"** published on June 6, 2019, which outlines the foot examination and tests to examine risk stratify and educate patients on foot care and footwear.

The guide is available online at http://www.ace-hta.gov.sg/public-data/our-guidance/Foot%20assessment%20in%20people%20with%20diabetes%20(June%202019).pdf or *via* the QR code below:

If your patient was previously under the care of TTSH/KTPH Vascular Lower Extremity Amputation Prevention (LEAPP) Clinic, and he/she **redevelops a DFU** within the next 12 months, he/she may be fast-tracked back for assessment. Please urgently refer him/her back to the TTSH/KTPH LEAPP Clinic at:

- Tan Tock Seng Hospital Clinic 2A (patient may call +65 6889 4258 to enquire)
- Khoo Teck Puat Hospital Clinic C31
- Alternatively, please contact their Call Center for assistance or more information:
    - +65 6357 7000 (TTSH)
    - +65 6555 8000 (KTPH)
    - Mondays to Fridays, 0830 to 1730 only

Thank you.
(Dr / Nurse / Podiatry to sign off)
On behalf of Diabetic Foot in Primary and Tertiary Care (DEFINITE) Care Program

Version 1.0 (18 Jan 2021)

Appendix 3: EQ5D Questionnaire

EQ-5D Health Questionnaire	
Mobility	
I have no problems in walking about	
I have slight problems in walking about	
I have moderate problems in walking about	
I have severe problems in walking about	
I am unable to walk about	
Self-care	
I have no problems washing or dressing myself	
I have slight problems washing or dressing myself	
I have moderate problems washing or dressing myself	
I have severe problems washing or dressing myself	
I am unable to wash or dress myself	
Usual Activities (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	
I have slight problems doing my usual activities	
I have moderate problems doing my usual activities	

I have severe problems doing my usual activities	
I am unable to do my usual activities	
Pain	
I have no pain or discomfort	
I have slight pain or discomfort	
I have moderate pain or discomfort	
I have severe pain or discomfort	
I have extreme pain or discomfort	
Anxiety/Depression	
I am not anxious or depressed	
I am slightly anxious or depressed	
I am moderately anxious or depressed	
I am severely anxious or depressed	
I am extremely anxious or depressed	
Health State	
We would like to know how good or bad your health is TODAY. The scale is numbered from 0 to 100. 100 means the best health you can imagine.	

0 means the worst health you can imagine. Mark an X on the scale to indicate how your health is TODAY. Now, please write the number you marked on the scale in the box below.	

Appendix 4: Diabetic Foot Ulcer Scale – Short Form (DFS-SF) Questionnaire

DFS-SF Questionnaire	
1. How much have your foot ulcer problems:[a]	
(a) Stopped you from doing the hobbies and recreational activities that you enjoy	
(b) Changed the kinds of hobbies and recreational activities that you enjoy doing	
(c) Stopped you from getting away for a holiday or weekend break	
(d) Made you choose a different kind of holiday or short break than you would have preferred	
(e) Meant that you had to spend more time planning and organising for leisure activities	
2. Because of your foot ulcer problems, how often have you felt:[b]	
(a) Fatigued or tired	
(b) Drained	
(c) That you had difficulty sleeping	
(d) Pain while walking or standing	
(e) Pain during the night	
3. Because of your foot ulcer problems, how often have you:[b]	

(a) Had to depend on others to help you look after yourself (such as washing and dressing yourself)	
(b) Had to depend on others to do household chores such as cooking, cleaning or laundry	
(c) Had to depend on others to get out of the house	
(d) Had to spend more time planning or organising your daily life	
(e) Felt that doing anything took longer than you would have liked	
4. Because of your foot ulcer problems, have you felt:[c]	
(a) Angry because you were not able to do what you wanted to do	
(b) Frustrated by others doing things for you when you would rather do things yourself	
(c) Frustrated because you were not able to do what you wanted to do	
(d) Worried that your ulcer(s) will never heal	
(e) Worried that you may have to have an amputation	
(f) Worried about injury to your feet	
(g) Depressed because you were not able to do what you wanted to do	
(h) Worried about getting ulcers in the future	
(i) Angry that this has happened to you	

(j) Frustrated because you have difficulty getting about	
5. Because of your foot ulcer problems, how often were you bothered by:[b]	
(a) Having to keep the weight off your foot ulcer	
(b) The amount of time involved in caring for your foot ulcer (including dressing changes, waiting for the district nurse, and keeping the ulcer clean)	
(c) The appearance, odour or leaking of your ulcer	
(d) Having to depend on others to help you care for your foot ulcer	
a 1 = not at all; 2 = a little bit; 3 = moderately; 4 = quite a bit; 5 = a great deal b 1 = none of the time; 2 = a little of the time; 3 = some of the time; 4 = most of the time; 5 = all of the time c 1 = not at all; 2 = slightly; 3 = moderately; 4 = quite a bit; 5 = extremely	

Appendix 5: Healthcare Provider Interview Prompts

- Date and place
- Age and experience in wound care
- Job title

General perceptions

- Tell me a little about your experience with patients with DFUs.
- What are the likely treatment outcomes?
- Do you know what wound imaging apps are?

Facilitators

- Have you used any wound imaging apps before? (if no, go to barriers).
- Tell me about a situation when you have tried to use wound imaging apps in your practice.
    - Why this episode?
    - What did you use it for?
    - What data did you collect?
    - How often?
- What motivated you as a healthcare provider to use wound apps?
- What elements of the intervention do you think are most important?
- Did you do any preparation before using wound apps to manage DFU?
- What is necessary for you to gain knowledge/experience and keep up-to-date about wound apps?

Barriers

- What is limiting you from using wound apps in your practice?
- What difficulties have you experienced when using wound apps?
- How did you solve it?
- Were there any challenges?
    - (financial, employees, technical)?

- Did you experience changes in the contact/bond with the patient?
- Do HCPs require education before use and how did that happen in the past?
- Do patients require education before use and how did that happen in the past?

Wound imaging apps in DFU Management

- Do you see the role of wound apps in DFU management?
    - How do you feel about apps used in DFU management?
- Could you tell me about whether you would be interested in using it?
- How do you perceive using wound apps to manage DFU?
- What information do you want to collect from the patient?
    - Education
    - Diabetic care plan
    - Wound care plan
    - Wound dressings used
    - Wound images
- What else would you like it to do?
- What would you change, take away or add?
- What about any problems or concerns you can see with this?
- How do wound apps affect the current DFU management process?
- Did you have to make any practical changes in consultations to enable the intervention? (time, follow-ups, other?)
- How about viewing large amount of data, e.g., wound dressing, wound description, and diabetes care?
- Do your patients see the role of wound apps in DFU management?
- How do your patients perceive using wound apps to manage DFU?
- Who do you think can be a candidate for this intervention? (What are the specific attributes of the patient that make them suitable or otherwise?)

Final questions

- Would you recommend wound apps to a colleague?
    - If so, what would you emphasize?
- Would you like to add anything?

- Would you like to elaborate on anything I asked?

Thank you for participating in this study. Your answers to these questions are very important to us, and we really appreciate dedicating your time to complete this interview. Please contact me if you have any questions or would like to discuss this topic further.

Appendix 6: In-Depth Interview Guideline for Patients

Thank you so much for participating in this study. As you know, we are conducting a study to explore patients' and caregivers' perspectives on the content and design elements of a mobile app for the management of DFUs.

We are very interested in learning more about your perspective on a phone health app for patients with diabetes wounds. The app allows doctors and nurses to get up-to-date information about your wound without you having to visit the clinic. We would like to ask you some questions about your use of technology and phone apps. Do you have a smartphone that you use?
Do you have WiFi access at home?
Are there any apps that you use on your phone? Which ones?
If there are apps they use: What do you like about the apps you already use?

If there are apps they use: What do you dislike about the apps you already use?
We would like to discuss the diabetes wound care app, eKare. Could we please show you a short video clip, after which you could tell us your opinion about it? *The interviewer shows a video clip demonstrating the use of eKare by a patient.* What challenges could this patient face when trying to do this? Would this be easy or difficult to do for a patient?

Do you ever take photos of your wound? If yes, what do you use it for? If no, why not?
Does your carer ever take photos of your wound? If yes, what do you and your carer use it for? If no, why not?

Would you be able to use a phone app the same way the patient in the video clip did? Would you be able to use your smartphone to take a photo through the app?
The app asks you to take a photo of your wound every time you or your carer clean it. Would you like to use this app to take photos of your wound every time you clean it? Why/why not?
Do you think this app could help you care for your wound? In what ways could it help you?
Is there anything else you would like to share with us?

Thank you very much for your time and participation.

Appendix 7: In-Depth Interview Guideline for Carers

Thank you so much for participating in this study. As you know, we are conducting a study to explore patients' and caregivers' perspectives on the content and design elements of a mobile app for the management of DFUs.

We are very interested in learning more about your perspective on a phone health app for carers of patients with diabetes wounds. The app allows doctors and nurses to get up-to-date information about the wound without requiring patients to visit the clinic. We would like to ask you some questions about your use of technology and phone apps. Do you have a smartphone that you use?
Do you have WiFi access at home?
Are there any apps that you use on your phone? Which ones?
If there are apps they use: What do you like about the apps you already use?
If there are apps they use: What do you dislike about the apps you already use?

We would like to discuss the diabetes wound care app, eKare. Could we please show you a short video clip, after which you could tell us your opinion about it? *The interviewer shows a video clip demonstrating the use of eKare by a patient.* What challenges could this patient face when trying to do this? Would this be easy or difficult to do for a patient?
What challenges could a carer face when trying to use the app to take photos of the wound? Would this be easy or difficult for a carer?
Do you ever take photos of the wound of the person you care for? If yes, what do you use it for? If no, why not?
Would you be able to use a phone app the same way the person in the video clip did? Would you be able to use your smartphone to take a photo through the app?

The app asks you to take a photo of the wound every time you clean it. Would you like to use this app to take photos of the wound every time you clean it? Why/why not?
Do you think this app could help you care for the wound of the person you care for? In what ways could it help you?
Is there anything else you would like to share with us?

Thank you very much for your time and participation.

Appendix 8: Case Report Form for EPOWS Pilot Clinical Study

VISIT DATE (MM-YYYY): ___________________________

Participant Code No:	....			
Date of Birth (MM-YYYY):	....		Age:	
Gender:	☐Male	☐Female	Height:	Weight:
Country of Origin:			Ethnicity:	

History (tick Yes OR No for each medical condition)

Please Tick Y/N	Medical Condition	List Current Medication(s) for the Medical Condition
☐Yes ☐No	Diabetes	Diabetes Med(s): Latest HbA1c level and date (MM-YYYY):
☐Yes ☐No	Hypertension (HTN)	HTN Med(s):
☐Yes ☐No	Coronary Artery Disease	Heart Disease Med(s): Previous CABG date (MM-YYYY): Previous PCI date (MM-YYYY):
☐Yes ☐No	Congestive Heart Failure	☐ None ☐ Mild symptoms and slight limitations during ordinary activity ☐ Marked limitation in activity due to symptoms, comfortable only at rest ☐ Severe limitations with symptoms even at rest
☐Yes ☐No	Kidney Disease	Kidney Disease Med(s): ☐ Normal Renal Function (eGFR ≥ 60) ☐ CKD 3 Moderately reduced kidney function (eGFR 30 59) ☐ CKD 4 Severely reduced kidney function (eGFR 15 29) ☐ CKD 5 End-stage renal failure (eGFR < 15) ☐ On dialysis ☐ Post-kidney transplant
☐Yes ☐No	Cerebrovascular Accident	CVA Med(s):
☐Yes ☐No	Chronic pulmonary disease	COPD Med(s): On home oxygen:
☐Yes ☐No	Peripheral Vascular disease	PVD Med(s):
☐Yes ☐No ☐Ex	Smoking history	Number of pack-years:

☐Yes ☐No	Other Medication	List:

Ambulatory Status

- ☐ Able to carry out all normal activities without restriction
- ☐ Restricted in strenuous activity but ambulatory and able to carry out light work
- ☐ Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours
- ☐ In a chair or bed for greater than 50% of the day but not bedridden
- ☐ Completely disabled, cannot carry out any self-care, totally confined to bed or chair

Living Status

- ☐ Home
- ☐ Rehab Unit
- ☐ Nursing Home
- ☐ Others

Limb Past History (answer yes or no to each item)

Right lower limb	Yes/No	**Left lower limb**	Yes/No
Existing foot deformity		Existing foot deformity	
Existing neuropathy		Existing neuropathy	
Previous Rx for PAD (and date)		Previous Rx for PAD (and date)	
Previous major amputation		Previous major amputation	
Previous minor amputation		Previous amputation	

Current Ulcer

Duration of current foot ulcer **(study wound)** __________weeks

Right extremity	Y / N / which type	Superficial (S) or deep (D)	Any infection
Ulcer/gangrene/amputation wound			
Single toe			
Multiple toes			
Forefoot amputation			
Dorsum of foot			
Heel			
Medial or lateral malleolus			

Superficial – involve only the skin and subcutaneous tissue, Deep – involve tendon, joint, fascia, bone

Left extremity	Y/N/which type	Superficial (S) or deep (D)	Any infection
Ulcer/gangrene/amputation wound			
Single toe			

Multiple toes			
Forefoot amputation			
Dorsum of foot			
Heel			
Medial or lateral malleolus			

Photograph wound ☐ No ☐Yes

Trace wound ☐ No, not done ☐Yes Area___________(cm^2)

Are there any **other** leg ulcers present? ☐No ☐Yes

If Yes, how many? __________ Sites: 1.________________ 2.__________________ 3.______________

Wound cleansed with: ____

Primary Dressing Type: ☐(Specify)
____

Exudate Type: Volume__________ ☐ Serous ☐ Haemoserous ☐ Sanguineous
☐

Purulent ☐ Odorous

Surrounding Skin & Tissue ☐ Healthy ☐ Bruised ☐ Dry/Scaly

☐ Hyperkeratosis ☐ Maceration ☐ Eczema

☐ Blistered ☐ Excoriated ☐ Erythema

☐ Cellulitis ☐ Induration ☐ Edema

☐ Haemosiderosis ☐ Callus ☐

Lipodermatosclerosis

☐ Atrophie Blanche ☐ Lymphoedema /papillomatous skin

Any wound **infection** diagnosed ☐No ☐Yes (Specify) ______________________________

Are you currently taking antibiotics? ☐No ☐Yes (Specify) ______________________________

PLEASE RATE THE ULCER PAIN EXPERIENCED BY THE SUBJECT USING THE VAS SCALE
Overall Pain

No Pain ____**Worst Pain**

0 **100**

Foot Arterial Supply

Right extremity		Left extremity	
ABPI (if any)		ABPI (if any)	

TPI (if any)		TPI (if any)	
Toe pressure			
Any revascularization procedure	Y/N	Any revascularization procedure	Y/N
Type of revascularization		Type of revascularization	
Date of revascularization		Date of revascularization	
Postprocedure TPI		Postprocedure TPI	
Postprocedure toe pressure		Postprocedure toe pressure	

Footwear

Right foot: _______________ Left foot: ______________

Foot Lesion Management

Management of foot lesion: (may choose more than one and specify date)

- ☐ Dressing only
- ☐ Bedside debridement
- ☐ Surgical debridement
- ☐ Single-toe amputation
- ☐ Multiple-toe amputation
- ☐ Transmetatarsal amputation
- ☐ Heel surgical debridement
- ☐ Primary major amputation

Billing Information

Cost of clinic visit	S$
Cost of inpatient stay	S$
Investigators cost	S$
Cost of consumables	S$
Cost of other services rendered Please specify:	S$
Additional information	

End of Report