PROGNOSTIC FACTOR OF LOWER LIMB AMPUTATION AMONG DIABETIC FOOT ULCER PATIENT IN KELANTAN FROM 2014 TO 2018

by

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TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST ABBREVIATIONS

Adj. HR	Adjusted Hazard Ratio
BMI	Body Mass Index
DM	Diabetes Mellitus
DFU	Diabetic Foot Ulcer
HR	Hazard Ratio
LML	Log-minus-log
LLA	Lower Limb Amputation
MOH	Ministry of Health
NCD	Non-Communicable Disease
NDR	National Diabetic Registry
NHMS	National Health Morbidity Survey
ODM	Oral Antidiabetic Medication
PAD	Peripheral Arterial Disease

LIST OF SYMBOLS

Symbol	Meaning
α	Alpha
β	Beta
≤	Equal and less than
≥	Equal and more than
kg	Kilogram
<	Less than
L	Litre
m	Metre
mmol	Millimole
>	More than
%	Percentage
p	*p*-value

ABSTRAK

FAKTOR-FAKTOR PROGNOSTIK BAGI AMPUTASI ANGGOTA TUBUH BAWAHAN DALAM KALANGAN PESAKIT ULSER KAKI DIABETIK DI KELANTAN BAGI TAHUN 2014 HINGGA 2018.

Latar Belakang: Amputasi atau pemotongan anggota tubuh bawahan adalah sesuatu yang serius dan mampu memendekkan jangka hayat seseorang pesakit ulser kaki diabetik. Namun, faktor prognostik yang membawa kepada amputasi anggota bawahan ini masih kurang diketahui dan perlu diterokai.

Objektif: Tujuan kajian ini adalah untuk menentukan masa bebas-amputasi median bagi kes ulser diabetik dan faktor-faktor prognostik amputasi anggota tubuh bawahan bagi pesakit ulser kaki diabetik di Kelantan bagi tahun 2014 hingga 2018.

Kaedah: Kajian retrospektif kohot ini telah dijalankan pada Oktober 2020 menggunakan data sekunder dari Registri Diabetik Kebangsaan (NDR). Sampel kes bagi kohot ini telah dikumpulkan dari 1 Januari 2014 sehingga 31 Disember 2018. Kohot ini kemudiannya telah diikuti sehingga 31 Disember 2019. Sebanyak 362 kes yang telah memenuhi kriteria kajian ini telah dianalisa dengn kajian deskriptif dan selanjutnya. Analisa masa bebas-amputasi telah dibuat mengunakan kaedah Kaplan Meier. Faktor prognostik pula telah ditentukan melalui kaedah univariat dan multivariat analisis menggunakan kaedah model Regresi Hazad-Proporsional Cox.

Keputusan: Kajian deskriptif telah menunjukkan kohot ini mempunyai purata (sisihan piawai) umur 59.0 (10.0) tahun. Sebanyak 61.6% merupakan pesakit perempuan menjadikan nisbah lelaki perempuan dalam kohot ini adalah 1: 1.6. Pesakit yang mempunyai Indeks Berat Badan (BMI) lebih dari 25kg/m^2 merupakan 55.9%. Seramai

37.3% pesakit mempunyai paras kolesterol-HDL yang tidak normal. Majoriti pesakit (92.8%) adalah bukan perokok.

Bagi status amputasi, seramai 66 (18.2%) orang pesakit ulser kaki diabetik telah menjalani amputasi anggota bawah. Manakala seramai 296 (81.8%) lagi tidak menjalani amputasi atau meninggal dunia sebelum menjalani amputasi. Oleh sebab kejadian amputasi yang tidak mencukupi, hanya masa bebas-amputasi purata dapat dikira iaitu sebanyak 59.35 bulan (95% CI: 56.63, 62.08).

Keputusan Analisa multivariat menunjukkan keputusan signifikan bagi 3 faktor iaitu umur, indeks berat badan yang obes, dan kandungan kolesterol-HDL. Pesakit berumur yang lebih tua (60 tahun dan ke atas) didapati mempunyai 52% kurang risiko dari amputasi anggota badan bawahan berbanding pesakit berumur kurang dari 60 tahun (Adj. HR 0.48; 95% CI: 0.27, 0.89; *p*-value = 0.019). Pesakit yang mempunyai indeks berat badan obes mempunyai 55% kurang risiko dari amputasi anggota badan bawahan berbanding pesakit indeks berat badan normal (Adj. HR 0.45; 95% CI: 0.22, 0.89; *p*-value = 0.039). Pesakit yang mempunyai kadar kolesterol-HDL tidak normal pula mempunyai 2 kali risiko yang lebih tinggi untuk amputasi anggota badan bawahan berbanding mereka yang mempunyai kadar kolesterol-HDL normal (Adj. HR 2.18; 95% CI: 1.21, 3.92; *p*-value = 0.009).

Kesimpulan: Dapatan tentang faktor prognostik dalam kajian ini membuka lembaran baru untuk kajian-kajian seterusnya dan boleh membantu untuk perancangan intervensi bagi pesakit ulser kaki diabetik bagi mengelakkan amputasi anggota badan bawahan.

Kata Kunci: masa bebas-amputasi, ulser kaki diabetic, amputasi anggota badan bawahan, faktor prognostik.

ABSTRACT

PROGNOSTIC FACTOR OF LOWER LIMB AMPUTATION AMONG DIABETIC FOOT ULCER PATIENT IN KELANTAN FROM 2014 TO 2018.

Background: Lower Limb Amputation (LLA) was a common complication of Diabetic Foot Ulcer (DFU). It was a serious problem as it may lead to a reduction in patient's survival. However, knowledge on the prognostic factor of LLA was still scarce and require further exploration.

Objectives: To determine the median amputation-free time among DFU patient and the prognostic factor of LLA among DFU patient in Kelantan from 2014 till 2018.

Methodology: A retrospective study was conducted in October 2020 using secondary data obtained from National Diabetic Registry (NDR). The cohort consisted of data accrued from January 1st, 2014, till December 31st, 2018. The cohort was then followed up till December 31st, 2019. Three hundred sixty-two cases that fulfilled the study criteria were analysed further. Amputation-free time was determined using Kaplan Meier Method. The prognostic factors were determined by univariate and multivariate analysis using the Cox Regression Proportional Hazard.

Result: Descriptive statistics showed that this cohort had a mean (SD) age of 59.0 (10.0) years old. Female patient consisted of 61.6%, which made the ratio of male to female is 1: 1.6. Patient with Obese BMI consisted of 55.9% of the sample. Patient with normal HDL- Cholesterol level consisted of 37.3% of the sample. The majority of the sample (92.8%) were non -smoker.

There were 66 (18.2%) DFU patient who had LLA in this study. At the same time, 296 (81.8%) did not undergo LLA or died before LLA. Due to insufficient event

of LLA, only mean amputation-free time was determined, which was 59.35 month (95% CI: 56.63, 62.08).

The result of Cox Proportional Hazard Regression revealed three significant findings. Patient with DFU aged 60 or more had 52% lesser risk to LLA compared to DFU patient aged less than 60 (Adj. HR 0.48; 95% CI: 0.27, 0.89; *p*-value = 0.019). Patients with DFU who was obese had a 55% lesser risk of LLA than patients with DFU who had normal BMI (Adj. HR 0.45; 95% CI: 0.22, 0.89; *p*-value = 0.039). Patients with abnormal HDL-Cholesterol had a 2.18 times higher risk to LLA than patients with normal HDL-Cholesterol levels (Adj. HR 2.18; 95% CI: 1.21, 3.92; *p*-value = 0.009).

Conclusion: The result on prognostic factor analysis opened a new horizon for future study, and it also assisted in intervention planning for DFU patient to prevent them from LLA.

Keywords: Amputation-Free Time, Diabetic Foot Ulcer, Lower Limb Amputation, Prognostic Factor

CHAPTER 1

INTRODUCTION

1.1 Diabetes Mellitus (DM)

DM is a chronic metabolic disease characterised by a condition where the patient cannot produce adequate insulin. Their body cannot utilise insulin due to the insulin resistance of the cells despite their ability to produce enough insulin. Hence, the glucose level will remain high in the blood, and it will cause various pathology at the microvascular and macrovascular level. (American Diabetes Assoc, 2014) DM was divided into two types which were type 1 and type 2. Type 1 was an autoimmune disease that usually happens among adolescents. Type 2 DM or non-insulin-dependent DM was typically the result of lifestyle factors such as high sugary meals, obesity, lack of physical activity, etc. (American Diabetes Assoc, 2014)

The global trend of DM was worrying. The total number of DM was projected to be increasing. By 2030, the overall number of DM was expected to rise to 578 million (10.2%), and by 2045, it will rise to 700 million (10.9%). DM also contributed to global NCD death as the 4th most common cause of NCD death that was 1.6 million (I D F Diabetes, 2019).

In Malaysia, National Health Morbidity Survey 2019 (NHMS 2019) reported an increase in Diabetes prevalence from 11.2% in 2011 to 18.3% in 2019. The most alarming fact in the NHMS 2019 was a spike from 5.1% in 2018 to 8.9% in 2019 (Institut Kesihatan Umum, 2020). This 75% increase was worrying because

undiagnosed DM might lead to untreated, elevated blood glucose for many years before. As a result, the patient might end up presented with symptoms and complications already taken place.

1.2 Diabetic Foot Ulcer (DFU)

DFU was one of the commonest diabetic complications. It was characterised as ulceration or destruction of foot tissues caused by neuropathy or peripheral arterial disease (PAD) among people with DM (Jaap J. van Netten, Sicco A. Bus, Jan Apelqvist, Benjamin A. Lipsky, Robert J. Hinchliffe, Frances Game, Gerry Rayman, and Nicolaas C. Schaper, 2019).

The pathophysiology of DFU was quite complex, given that multiple conditions can lead to sufficient cause to the occurrence of DFU. These factors were neuropathy, PAD, immunopathy, mechanical stress and neuroarthropathy. Once an ulcer develops, these conditions may also exacerbate the ulcer by predisposing its infection and poor healing. Therefore, when it was not salvageable, it would be amputated.

International Diabetic Federation reported the global prevalence of DFU to be 6.3%, but it could range up to 14%(Abdissa *et al.*, 2020; Mariam *et al.*, 2017; Zhang *et al.*, 2017). The Prevalence of DFU in Malaysia ranged from 5-10%, but in a study conducted in 2018, the prevalence of DFU could go up to 42% among diabetic patient in Kuala Lumpur (Hadi *et al.*, 2019; Jamani, N. A. and Muhammad, 2018).

1.3 Lower Limb Amputation (LLA)

The term "lower limb amputation" (LLA) refers to removing one or more lower limb sections. It was a surgery done if the infected DFU become complicated and no more salvageable. It was divided into two types, major amputation (above the ankle) or minor amputation (proximal to ankle) (Alvarsson *et al.*, 2012; Esquenazi and Yoo, 2016).

An estimated 70% of LLA case across the globe occurred due to diabetic condition (I D F Diabetes, 2019). Its global incidence varied from 46.1 to 9600 cases for every 100 000 population with Diabetes (Moxey *et al.*, 2011). In Malaysia, 4.3% Diabetic patient was reported to have LLA (Letchuman *et al.*, 2010). DFU and LLA were considered independent risk factors to mortality (Armstrong *et al.*, 2020).

Median time to amputation also varied from 2 to 14 months, depending on the type of amputation (Lin *et al.*, 2020; Nelson *et al.*, 2016). Works of literature come in conflict as some study suggested 1-year amputation rate for all amputation can go up to 88%(Ab Rahman *et al.*, 2016), but another reported that 1-year amputation-free survival for all amputation among DFU patient was 65.9% (Won *et al.*, 2014)

1.4 Malaysia National Diabetic Registry (NDR)

According to the National Health Morbidity Survey 2011, MOH health clinics bore the most burden of treating Diabetic patient in Malaysia, which was 56.0%. MOH hospitals (24.6%) and the rest, including private clinics, were around 20%. Before NDR, MOH started to perform manual data collection with a paper-based return to register the patient under their follow up. However, the manual process had a lot of limitation. Therefore, MOH started to embark on a more systematic way of collecting

data on the quality of care and monitoring of Diabetes in Malaysia by establishing the NDR.

The objectives behind the establishment of NDR were:

1. To acquire reliable clinical data, which is an improvement to previously manual audit systems was made.
2. To allow for monitoring glucose control and clinical outcomes in diabetic patients treated at MOH health clinics.
3. To enable comparison of data throughout time and across geographical regions
4. To allow research to be conducted to improve diabetic treatment and the quality of care offered to patients.

According to the latest National Diabetes Registry Report 2013-2019, there were around 897 421 active diabetes patients in NDR out of 1614 363 patients registered in NDR where the majority of them were having type 2 DM (99.3%), female (57.1%) and Malay ethnicity (59.2%). The system's limitation was that it highly depended on the documentation from health staff from the health facility involved. Still, the MOH complemented it by continuous training and monitoring at the state and district level to ensure that the staff involved in entering the data was well trained and well versed with the system (Arunah Chandran, Mohd Nazri Abdullah, 2019).

1.5 Problem Statement and Rationale

The increasing undiagnosed DM was a worrying trend as it was expected that more patient had already established complication upon diagnosis. There was currently a limited study that analysed median amputation-free time of LLA among DFU patient in Malaysia. This proposed study was a state-level study that might found further

prognostic factor due to its inclusiveness. This study also explored additional protective effect from the treatment of DM and Statin to prevent LLA. It was hoped that this study might assist Kelantan Health Department and their clinician to strategise better in term of prevention and management of LLA among its patients.

1.6 Research Questions

i. What is the median amputation-free time of LLA among patients with DFU in Kelantan from 2014-2018?

ii. What are the prognostic factors of LLA among patient with DFU in Kelantan from 2014-2018?

1.7 Objectives

1.7.1 General Objectives

To determine the median amputation-free time of LLA and its prognostic factors among patient with DFU in Kelantan from 2014-2018

1.7.2 Specific Objectives

i. To determine the median amputation-free time of LLA among patient with DFU in Kelantan from 2014-2018.

ii. To determine the prognostic factors of LLA among patient with DFU in Kelantan from 2014-2018

1.8 Research Hypothesis

i. Null hypothesis

There are no associations between prognostic factors (sociodemographic, clinical, biochemical and treatment) with LLA among DFU patients in Kelantan.

ii. Alternative hypothesis

There are associations between prognostic factors (sociodemographic, clinical, biochemical and treatment) with LLA among DFU patients in Kelantan.

CHAPTER 2

LITERATURE REVIEW

2.1 Epidemiology of DFU

DFU was more common in type 2 DM due to its long latency period than type 1 DM. DFU was believed to be present in 6.3% of the world's population. In Asia specifically, the prevalence reported was 5.5%. Belgium was reported to have the highest prevalence of DFU, which was 16.6%. The cause of high prevalence in Belgium was said due to low incentive in DFU prevention, where individuals mainly supported the cost, and when the patient had DFU, then the healthcare system would support the cost of treatment (Zhang *et al.*, 2017).

In Malaysia, a study was conducted in an urban primary care clinic in Kuala Lumpur. The study found that the prevalence of DFU was 42.2%, by which there was significantly low awareness of foot problem among its study participant (Jamani, N. A. and Muhammad, 2018). Despite higher treatment of Diabetes uptake in urban, the overall blood glucose control was reported to remain low at only 21.8%. (Ho BK, Jasvindar K, Gurpreet K, Ambigga D, Suthahar A, Cheong SM, 2020). A higher number of DFU was expected in rural area due to delayed treatment and logistic difficulties (Kow *et al.*, 2019).

D. G. Armstrong et al. (2017) found that the most significant risk factor to a DFU was a healed DFU. This was because the neuropathy and PAD persist and readily cause another ulcer if proper foot care was not established.

Zhang et al. (2017) reported that 25% of diabetic patients would develop diabetic foot feet in their lifetime. 85% of poorly healed ulcers would end up with LLA (Boulton, 2010). Similarly, Hadi et al. (2019) reported that DFU was the leading cause of LLA in Malaysia.

2.2 Pathophysiology of DFU

The pathophysiology of DFU was quite complex, given that multiple conditions can lead to the occurrence of DFU. These conditions were mainly neuropathy and PAD. Plus, other factors such as immunopathy, mechanical stress, and neuroarthropathy (Syafril, 2018).

Neuropathy was an impairment of nerve activity, leading to altered body function in sensory, motor, and even autonomic function. The development of neuropathy in a diabetic patient takes a long period of up to 10 years. However, it remained a common complication as the study reported half of the diabetic patients in the study sample had peripheral neuropathy(Selvarajah, 2012). The high level of glucose would damage the nerve that innervates the lower limbs, leading to the poor sensory function of the affected foot. As a result, the foot could get an unnoticed injury, leading to ulceration (Syafril, 2018)(Selvarajah, 2012).

PAD was another main factor in the development of DFU. It was characterised by atherosclerosis of the vessel, which led to ischaemia and poor perfusion of the tissue. In addition, atherosclerosis may occur due to endothelial and smooth muscle dysfunction due to oxidative stress created by the hyperglycaemic condition (Creager *et al.*, 2003; Noor *et al.*, 2015; Syafril, 2018).

Subsequently, an infection may develop, and the high glucose condition would be more favourable for bacterial growth. In addition, the inadequate vascular supply due to PAD may lead to delayed healing and exacerbate the infection. Finally, the infection could be life-threatening, by which the treating clinician may resort to LLA to save the affected patient's life (Singh *et al.*, 2013).

2.3 The economic impact of DFU

DFU also posed a significant healthcare burden and posed the most cost out of the other diabetic complications. A prospective study in Sweden reported expenditure cost for DFU without amputation until complete healing was approximately 37% of total healthcare cost. Another study in the United States by Driver et al. (2010) reported USD 174 billion spent on diabetes and its complication. Around 30% of the complication were linked to DFU (Driver *et al.*, 2010; Raghav *et al.*, 2018).

Another local study in Terengganu, Malaysia, reported that treating 182 patients admitted for acute infected DFU would cost around USD 11 000, where half of the expenditure (50.3%) was used to administer antibiotics. The high cost of antibiotics was due to the polymicrobial infection in DFU and the long duration of more severe conditions requiring parenteral, intravenous antibiotic (AWC *et al.*, 2014). However, the study in Terengganu did not include the overall cost of care once the patient was discharged, which was speculated to be higher as it would involve proper footwear, dressings, and other prevention from ulcer recurrence.

2.4 LLA among DFU patient

LLA was the common sequelae of DFU, and it was a common marker of poor health outcome for diabetic patient. It was defined as the amputation of a part or many

sections of a lower limb (Esquenazi and Yoo, 2016). When the limb with DFU becomes infected or worsening limb ischaemia, it became no more salvageable and life-threatening to the patient; hence, amputation choice was inevitable. There were two types of LLA: major and minor amputations. Major category was when the level of amputation was proximal to the ankle. The minor category was when the amputation was distal to the ankle (Esquenazi and Yoo, 2016).

A diabetic patient was 25 times more likely to suffer leg amputation compared to a non-diabetic person. An estimated 70% of LLA cases across the globe occurred due to diabetic condition (I D F Diabetes, 2019). However, incidences of LLA varied around the world. A study in the United Kingdom was conducted to look at the variation of incidence of LLA globally, and he reported that the incidence of LLA, regardless of its type, varied from 46.1 to 9600 cases for every 100 000 population with Diabetes (Moxey *et al.*, 2011).

In Malaysia, Letchuman et al. (2010) analysed the data from a cross-sectional population-based national study conducted in 2006 involving nearly 60 000 samples of eligible adults 18 years and above. Their analysis found that 4.3% of patients with known diabetes had amputation of the lower limb. .The incidence of re-amputation was relatively high, which recorded to be almost 20%, according to Borkosky and Roukis (2012). Hence, it was prudent to prevent LLA among DFU patients, especially when undiagnosed diabetes was rising. The survival rate of lower limb amputees varied in terms of which level of amputation brings better survival. Still, the advancement of medical treatment of diabetes and rehabilitation of amputees did improve lower limb amputees (Kulkarni *et al.*, 2006).

D. G. Armstrong et al. (2020) reemphasised their study in 2007 about the significant impact on mortality rate by DFU and LLA. They collected the 5-year mortality data after their research in 2007 and calculated the pool mean. Their report in 2020 revealed that overall LLA led to a higher 5-year mortality rate than all cancer combined. The 5-year mortality by major LLA led to 56.6%, and the minor LLA lead to 46.2% of mortality. Hence, they concluded that both DFU and LLA was an independent risk factor for premature mortality.

2.5 Amputation time of LLA among DFU patient

Various literature had reported median time with regards to LLA among diabetic foot. Among term used was time to amputation, amputation time, amputation-free time, and amputation-free survival.

In a retrospective study conducted in Korea, Won et al. (2014) sought to determine the 1-year amputation-free survival rate and LLA risk factor among patients with DFU. One hundred seventy-three DFU patient was included in the study sample. The study revealed that the 1-year amputation-free survival rate was 65.9% for all amputation, and for major amputation, the 1-year amputation-free survival rate was 93.1%.

In another single-centre retrospective study conducted in Kelantan, Malaysia, Ab Rahman et al. (2016) aimed to determine the amputation-free probability for major amputation and prognostic factors to major LLA among DFU patient in a tertiary teaching hospital. Two hundred thirty-one were enrolled in the study sample and was followed up for a year. They reported that 28 (12.1%) had a major amputation at the end of the study. Minor amputation was included under censored observation in this

study as it was not part of their objective. But they still reported 177 (76.6%) patients in their study sample experience a minor amputation.

Lin et al.(2020) conducted a retrospective analysis utilising data from the California Office of State-wide Health Planning and Development. Patients with lower limb ulcers identified with PAD, DM, or both who had their first amputation after being diagnosed with lower limb ulcers were included in the study's cohort. The cohort was followed up whether the patient in the cohort had a subsequent amputation, either minor or major. The result showed that patient with DM alone recorded the median time to subsequent minor amputation of 5.9 months. The median time to major amputation was reported as 14.1 months. The median time to major amputation for all patient in the cohort was 12.9 months. Overall major amputation rate was reported as 5.1% by which patient with PAD and DM has a higher rate of amputation (6.3%) compared to DM alone (5.2%) (Lin *et al.*, 2020).

A prospective cohort study where a subsample from a cross-sectional survey in England was followed up for 12 months to determine the prognosis of infected DFU. The subsample consisted 299 of patients aged 18 years old and above with DM and infected DFU planned to be treated with an antibiotic. In that study, Nelson et al. (2016) reported the median time to ipsilateral amputation after diagnosis of DFU was 2 months. Skoutas et al. (2009) reported 26.1% of re-amputation due to DFU within 18 months.

2.6 The prognostic factor of LLA among DFU patient

The past decade had shown tremendous improvement in the rate of non-traumatic amputation among diabetic patients. This trend was postulated due to the advancement

of care, and early screening and treatment commenced upon a diabetic patient. However, the increasing prevalence of undiagnosed diabetes remained a worry as the patient may present with infected DFU requiring amputation straightaway. The prognostic factor was important for identification. It would guide the clinician and public health physician to decide on the patient's treatment and strategies for amputation prevention in the population. There were many factors found in the literature that can hasten or delay amputation.

2.6.1 Sex

Generally, females had a longer life expectancy but a lesser quality of life due to higher morbidity than males. Sex differences were linked to the difference in behaviour between males and females, such as males were more likely to be heavy smoker or regular alcoholic drinker. A male patient was also less likely to go for healthcare visits than females, resulting in delayed treatment and fatal complication. On the other hand, some literature also reported that females often had a poor quality of blood sugar control despite better health-seeking behaviour. This finding was because of female inner conflict, such as their common belief to put family first before her personal needs. Poor blood glucose control might eventually lead to complication such as LLA (Crimmins *et al.*, 2019; Siddiqui *et al.*, 2013).

A retrospective study in Malaysia was conducted in University Science Malaysia among hospitalised diabetic foot patients to determine the median amputation-free time and its prognostic factor. The study accrual time was five years from January 1st, 2007, until December 31st, 2011, and this cohort was followed up for one year whether the patient had a major amputation or not. Minor amputation was

censored in this study, and it revealed that female had a higher risk of LLA (Adj. HR 4.77, 95% CI 1.52, 14.96).

However, another study in Canada showed the opposite result. The study was conducted as a prospective population-based cohort study. The starting time was when the patient was diagnosed with DM and followed up for seven years until the event of interest. The event of interest was divided into primary outcome (minor amputation) and secondary outcome (major amputation). The study reported that men were more likely than women to have their lower extremities amputated. (HR 1.87, 95%: CI 1.79–1.96) (Amin *et al.*, 2014).

A study in Korea showed mixed result. This retrospective study was conducted in a hospital in Korea to determine the 1-amputation-free survival rate and its risk factor. Its findings revealed that being male was a protective factor for all amputations compared to females (HR 0.8, 95% CI: 0.97, 1.03) and major amputation (HR 0.36, 95% CI: 0.10, 1.26) specifically. But the result was not significant (Won *et al.*, 2014).

2.6.2 Age

Ageing was established as a factor that delayed wound healing. Wound healing required four phases which were haemostasis, inflammation, proliferation, and remodelling. Delays in inflammation, infiltration of macrophage, and epithelisation in the elderly significantly impact each phase of the wound healing stages, resulting in poor wound healing, further risk the person to LLA (Guo and DiPietro, 2010; Harker, 2006).

Morbach et al. (2012) conducted a retrospective study in which a cohort of diabetic foot patient containing 247 patients with DFU without major amputation

previously from a single centre was followed up for ten years. The result revealed that every increase in age by 1 unit year would increase LLA risk (HR 1.08, 95% CI: 1.06, 1.10).

In their retrospective study, Ab Rahman et al. (2016) also reported that older age diagnosed with DFU had a higher risk of major amputation (HR 1.05, 95% CI: 1.00, 1.09).

In a retrospective analysis in Japan by Kaneko et al. (2018), they also reported that age ≥ 60 was independently associated with amputation (HR 1.09 95% CI: 1.02, 1.16), and the result was significant.

However, some literature finding showed older age as a protective factor. For example, a substudy conducted in England, where 1-year follow up was conducted among 299 samples. The aim was to determine the prognosis and risk factor of infected DFU. The study revealed that after categorising age, the incidence of healing was higher in older patients (HR 1.02; 95% CI: 1.01, 1.04). However, the author suspected it to be a spurious relationship because the finding was inconsistent when age was analysed as a continuous variable.

A prospective population-based cohort study was conducted in South London, the UK, where 253 people recruited from all community chiropody and hospital foot clinic within 5 National Health Service Health Authorities. The mean age of the sample was 68.8 (10.9) years old. However, the result revealed that age was not a significant prognostic factor to LLA, although it showed a protective hazard ratio (HR 0.99, 95% CI: 0.97, 1.02) (Winkley *et al.*, 2007). Similarly, Ikura et al. (2015) reported a similar finding in their single-centre historical cohort study. The mean age of its sample was 62 (14) years old. Ikura et al. stated that age was not a significant predictor for LLA.

2.6.3 Ethnicity

Ethnicity refers to a certain construct consisting of biology, culture, language, religion, and even distinct health belief or behaviour. Therefore, it became a significant variable for epidemiologists as certain health beliefs or behaviours could be unique to certain ethnicities like health-seeking behaviour or the more trust put on the traditional mode of treatment despite its non-scientific nature than modern medicine (Chen, 1981). Moreover, in some countries, racial inequities and systemic discrimination against certain races might affect the quality of healthcare service they receive. Hence, the glucose control would become poorer leading to more complication like DFU and LLA (Williams and Rucker, 2000).

Malaysia was a multi-ethnic nation by which Malay ethnicity holds the majority in number, followed by Chinese, Indian, and others. In the south of West Malaysia, Singapore had almost the same ethnic composition, but the Chinese were the majority race, followed by Malay and Indian. Lim et al. (2021) used 10-year administrative data gathered by the Ministry of Health Singapore in their study. They reported that Malay had the highest risk to LLA (HR 165.95, 95% CI: 54. 24, 507.75), followed by Indian ethnicity (HR 72.17, 95% CI: 17.57, 296.40) and both Malay and Indian had a higher risk to LLA compared to the Chinese race.

In New Zealand, a prospective study was conducted involving a large cohort of multi-ethnic patients reported that despite Indian people had an incidence rate of 0.68 per 1000 person-years, it posed a statistically significant lower risk to LLA compared to European ethnicity in both demographic (HR 0.39, 95% CI: 0.22, 0.67) and clinical model (HR 0.48, 95% CI: 0.27, 0.83).

2.6.4 Body Mass Index (BMI)

BMI was one of the ways to categorise a person's weight. The calculation was done by multiplying the person's weight in kilogrammes by the square of his or her height in metres. The result will be in the 'kg/$m^{2'}$ unit, categorised into underweight, normal weight, overweight, and obese. Although it was not directly correlated to body fat content, BMI had established itself as an important predictor of many cardiovascular disease and non-communicable diseases.

There were terms called 'obesity paradox' where BMI increase led to a lesser risk to non-communicable diseases and complications. Several mechanisms were suggested, like having enlarged muscle mass might also manifest as high BMI and the mobilisation of endothelial progenitor cells, leading to atherogenesis. The mobilisation of endothelial progenitor cell protects the person from vasculopathy which was one of the precursors to DFU and LLA (Hainer and Aldhoon-Hainerová, 2013).

A retrospective study using a cohort of non-elderly diabetic men in the USA reported this paradox. A Higher BMI ≥ of 30kg/m2 was said to have a lesser risk to LLA, and having a lower BMI was more likely to have any LLA (HR 3.11, 95% CI 1.67, 5.78). All the result reported was statistically significant (Sohn et al., 2012).

Higashi et al. (2019) conducted a two-year observational retrospective cohort study in Japan to evaluate amputation predictors in people with diabetes who were taking antiplatelet medication for PAD. In that study, they compared the between-group with BMI ≥ 25 and BMI < 25, they reported that BMI < 25 had a higher risk to LLA (HR 1.36 95% CI: 0.54, 3.40), but the result was not statistically significant. Similar finding reported by Kaneko et al. (2018). they performed a retrospective analysis using a nationwide claims database in Japan that reported a protective hazard

ratio (HR 0.98 95% CI: 0.88, 1.10) for every 1kg/m^2 increase of BMI, but the result was not statistically significant.

2.6.5 Smoking

The impact of smoking on vascular-related was undisputable. There were several mechanisms to explain how smoking can lead to a higher risk of limb loss. First was the vasoconstriction effect of nicotine and its stimulant effect that increased heart rate by 20 beats per minute for every cigarette. Increasing the heart rate against vasoconstrictive arteries will be more difficult for the heart because it pumps against a high-pressured lumen. Second, smoking can also accelerate the hardening and narrowing of the vessel, which interfere with the blood flow, which was important for wound healing. Finally, smoking also increased LDL cholesterol levels in the blood and decreased the level of HDL cholesterol. This condition would permit atheroma formation, which led to PAD, a precursor to DFU and LLA (Rosemont, 2019).

Robinson et al. (2016), in their study on the risk of LLA among people with type 2 DM, also reported that both ex-smoker (HR 1.26, 95% CI: 1.09, 1.47) and current smoker (HR 1.63 95% CI: 1.35, 1.97) had increased risk to LLA compared to a non-smoker.

Similarly, in their study on the effect of smoking cessation, J. Armstrong et al. (2014) reported that patients who quit smoking would improve their amputation-free time and had a lesser risk to LLA (HR 0.4 95% CI, 0.19, 0.83). The result in this study was statistically significant.

Won et al. (2014) conducted a retrospective study among patient with diabetic ulcer to determine the 1-year survival rate and 1-year amputation-free survival in

Korea. This study reported that smoking among DFU patients would increase the risk of all types of amputation (HR 1.07 95% CI: 0.59, 1.97), but the result was not significant.

In a ten year follow up study by Callaghan et al. (2011), in a diabetic cohort, researchers wanted to see if there was a link between triglycerides and lower extremity amputation. They reported that diabetic patients currently smoking had a higher risk of lower extremities amputation (HR 1.24 95% CI 0.99, 1.55), but the result was not statistically significant.

2.6.6 Duration of Diabetes.

The precursor of DFU and LLA, such as PAD and neuropathy, require years to develop. Neuropathy can take place after 8-12 years of type 2 DM diagnosis. Hence, the more DM's duration, the more likely the patient would develop DFU and LLA (Syafril, 2018).

Ab Rahman et al. (2016) reported in a retrospective study in a tertiary teaching hospital that the duration of DM ≥ 10 years brought a higher risk to LLA than DM < 10 years. Another study in Scotland used Scottish Care Information Diabetes, where the study includes diabetic patient with high-risk foot who never had any amputation in their cohort of sample. The study reported that a longer diabetes duration would shorten the amputation-free survival time (Vadiveloo *et al.*, 2018). Callaghan et al. (2011) also reported that duration of more than 10 years had a higher risk to LLA among diabetic patient (HR 1.94 95% CI 1.65, 2.28), and the risk increased further if the duration was more than 20 years (HR 2.38 95% CI 1.96, 2.88).

A longitudinal study was conducted in Germany that analysed 3892 patients with type 2 diabetes with the first diagnosis of diabetic foot syndrome. It aimed to determine the amputation risk and factor influencing amputation among diabetic foot patients. One of the findings was that a longer duration of diabetes posed a higher risk to LLA ((Pscherer *et al.*, 2012).

2.6.7 Ischaemic Heart Disease

Atherosclerosis and heart failure in ischaemic heart disease may influence the oxygenation of the tissue. The reduced cardiac output in heart disease may disrupt the effectiveness of the peripheral circulation, reduce oxygen delivery, therefore causing chronic hypoxia to the tissue. Although acute hypoxia may stimulate wound healing initially, chronic hypoxia may cause the opposite, especially in chronic wounds such as DFU. Hence if the circulation is disrupted, it will lead to chronic hypoxia and delay the wound healing (Ditata, 2016; Hajime Abe, Hiroaki Semba, 2017; Schreml *et al.*, 2010). The delayed healing of wound would bring higher risk to LLA

In a prospective study in Iran, Niakan et al. (2020) found that diabetic comorbidities and complication such as ischaemic heart disease led to a higher risk of DFU formation (HR 6.52 95% CI, 1.04, 20.11). Similarly, Yazdanpanah et al. (2018), in their study to determine the risk factor associated with DFU, also revealed that heart disease by which in their case, myocardial infarction, was associated with a higher risk of DFU formation (HR 4.53, 95% CI, 1.08, 19.01)

In their retrospective study in Japan, Higashi et al. (2019) sought to determine risk factors for major amputation among patients with diabetes and PAD who received

antiplatelet therapy. They discovered that among diabetic individuals with heart disease, the chance of any amputation was increased. (HR 3.32 95% CI 1.39, 9.30).

In another study in Thailand, the researcher retrospectively reviewed all admission medical records due to DFU in a tertiary hospital from 2014-2018. In this study, ischaemic heart disease was grouped under cardiovascular disease together with heart failure. In addition, the amputation-free survival rate was also defined as the percentage of patients who survived without major amputation. The result revealed that cardiovascular disease was associated with unhealed DFU (Thewjitcharoen *et al.*, 2020).

2.6.8 Dyslipidaemia

Dyslipidaemia is a condition characterised by an abnormal level of serum cholesterol, LDL-Cholesterol, HDL-Cholesterol and Triglyceride. An increased level of LDL-cholesterol is important in developing atherosclerosis and PAD, leading to poor blood flow and arterial insufficiency. Hence, this condition would lead to poor healing, increasing the risk of LLA in DFU patients (Hirsch and Gotto, 2002).

In a prospective study conducted in Nekemte Hospital in Nigeria, Bekele and Chelkeba (2020) sought to determine the amputation rate of patient with DFU and its associated factor. In this study, the researcher used one variable: comorbidity, a combination of hypertension, Coronary Heart Disease, Dyslipidaemia, and PAD. The result showed that patient with comorbidity had a higher risk of LLA (HR 2.74, 95% CI 0.70, 7.47), but the result was not statistically significant.

In a retrospective study conducted in Germany, Richter et al. (2018) aimed to explore the impact of DM type on treatment and its impact on the outcome of PAD

patient. One of the events of interest was limb amputation. The result showed that dyslipidaemia had a statistically significant lower risk of LLA (HR 0.74, 95% CI, 0.70, 0.77).

The result by Richter et al. was similar to another study in the previous year by Malyar et al. (2016), which used the same database from BARMER GEK, German-based health insurance. Malyar et al. (2016), in their retrospective study, also reported that patient with dyslipidaemia had a lower risk of LLA (HR 0.70, 95% CI, 0.66, .74). However, both articles did not explain the reason behind their finding.

2.6.9 Hypertension

The formation of atherosclerosis is one of the pathologies that happen in diabetic-induced vasculopathy. Hypertension may accelerate the occurrence of atherosclerosis through several mechanisms. The high blood pressure in hypertension would be compensated by the increased growth of vascular smooth muscle, leading to a decrease in lumen size and medial thickening. This condition will lead to further reduced blood flow, disrupts the oxygenation of tissues, and creates oxidative stress, which further exacerbates the vessel's damage (Martinez-Quinones *et al.*, 2018; Virdis *et al.*, 2011).

In Japan, Higashi et al. (2019) conducted a prospective cohort study among patients with diabetes and PAD. The 2-year nationwide study included 1745 centre in Japan where around 10 000 was followed up. The study revealed that being diagnosed with hypertension brought a higher risk to LLA than patient with no hypertension, but the result was not statistically significant at multivariable analysis.

Bekele and Chelkeba (2020) conducted a prospective study in Nekemte Hospital in Nigeria to determine the amputation rate of patient with DFU and its

associated factor. In this study, the researcher used one variable: comorbidity, a combination of hypertension, dyslipidaemia, coronary heart disease, and peripheral vascular disease. The result showed that patient with comorbidity had a higher risk of LLA (HR 2.74, 95% CI 0.70, 7.47), but the result was not statistically significant.

2.6.10 Stroke/Cerebrovascular disease (CeVD)

Stroke or Cerebrovascular disease is another factor that may lead to LLA. The mechanism suggested was that the sensation was altered on the affected side in stroke. Hence, the disrupted sensation may lead to unrealised trauma. In addition, the affected limb also may have reduced blood flow due to the lack of muscles used. These factors would further deteriorate the wound, delay its healing, thus putting the limb at risk of amputation (Garrison *et al.*, 1986).

In their study, Higashi et al. (2019) sought to determine the risk factors of major amputation in a patient with diabetes who undergone antiplatelet therapy for PAD. They reported that cerebrovascular accident and heart disease posed a higher risk of major amputation (HR 3.32, 95% 1.19, 9.30).

2.6.11 Nephropathy

Nephropathy or chronic kidney disease is one of the most common complications of DM. It also contributes to wound disruption more compared to a patient with normal kidney function. Delayed wound healing by chronic kidney disease occurs because of the delayed granulation rate, low vascularisation, and cell proliferation rate. Moreover, in patients with end-stage renal disease (ESRD), the uraemic condition further disrupts wound healing by reducing fibroblast proliferation and collagen production. ESRD patient who underwent dialysis also predisposes them to loss of protein which is

important for wound healing (Maroz and Simman, 2013). The delayed wound healing further put DFU patient at risk of amputation.

Malyar et al., 2016 conducted a retrospective study using nationwide data from BARMER GEK, large German health insurance, on the short- and long-term outcome of a patient with diabetic foot syndrome and PAD in Germany. The study revealed that chronic kidney disease was a significant predictor of LLA (HR 1.3 95% CI 1.24, 1.37).

A study by Higashi et al. (2019) based in Japan sought to determine the risk factors of major amputation in a patient with diabetes who undergone antiplatelet therapy for PAD. They reported that having chronic kidney disease was a significant risk factor for any amputation (HR 4.19 95% CI 1.95, 8.97).

2.6.12 Serum Hba1c

Serum Hba1c is used as a marker for glucose control among patient with diabetes. A value of 6.5% or more is an indicator of uncontrolled blood glucose level, requiring further intervention or modification for the patient to avoid chronic hyperglycaemia complications (Malaysia, 2020). Uncontrolled blood glucose will lead to sorbitol accumulation, affecting nerve conduction, hence explaining the insensate neuropathy. The condition also may lead to delayed diagnosis of DFU, which may further risk the foot to amputation (Syafril, 2018).

Callaghan et al. (2011) conducted a 10-year follow-up study among the diabetic cohort to determine factor associated with lower-extremity amputation. They revealed that increasing HbA1c value would increase the risk of LLA. The study classified uncontrolled Hba1c into three categories which were 7 to 8 (HR 1.45 95%