Original Article

Review of Transmetatarsal Amputations in the Management of Peripheral Arterial Disease in an Asian Population

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Objective: To evaluate outcomes after transmetatarsal amputation (TMA) in peripheral arterial disease (PAD) limb salvage in an Asian population and identify risk factors associated with TMA failure.

Methodology: A retrospective review of 147 patients with PAD, who had undergone TMA between 2008 and 2014, was carried out. Univariate and multivariate analysis were used to identify predictors of TMA failure. Kaplan–Meier survival analysis was used to calculate major amputation and all-cause mortality rates.

Results: The mean age was 66 years. 92% were diabetic patients and 78% had preceded angioplasty. 56% of TMAs were healed via secondary intention, 8% required subsequent split-thickness skin graft closure, 24% required further debridement while 37% had wounds, which failed to heal and required below-knee amputations (BKA). Multivariate analysis showed that diabetes is the only independent predictor of TMA failure (odds ratio (OR) 7.11, p=0.064). Patients with TMA failure were at increased risk of developing nosocomial infections (p=0.025) and faced a higher risk of 30-day re-admission rate (p=0.002).

Conclusion: The success rate for PAD limb salvage TMA was 63% and diabetes was an independent predictor of TMA failure. Patients with TMA failure were at increased risks of nosocomial infections, and 30-day re-admissions;
hence the risks and benefits of TMA for diabetic foot limb salvage must be individualized for each patient.

Introduction

Peripheral arterial disease (PAD) affects more than 200 million people worldwide and it is associated with significant rates of cardiovascular morbidity and mortality. It is the third leading cause of atherosclerotic vascular morbidity after coronary heart disease and stroke.[1,2] This disease burden is expected to increase further, with increased exposure to chronic risk factors and an aging population.[3] Patients with PAD also face about a threefold higher risk of mortality and major cardiovascular events.[4]

PAD affects about 1 in 10 people aged 70 and 1 in 6 people older than 80 years old.[5] The true incidence of the disease may be higher than the estimated number given that most patients are asymptomatic and have a screening ankle–brachial index (ABI) of 0.90 with a sensitivity of less than 80%.[6] In Asia, the higher incidence of diabetes mellitus (DM) has aggravated a greater incidence of peripheral vascular disease.[7] The combination of PAD and DM is associated with significantly poorer healing rates and risks of limb loss.[8]

In patients with PAD and forefoot sepsis or tissue loss, transmetatarsal amputation (TMA) is a viable option to avoid major amputation of a lower limb. TMA, compared to a below-knee amputation (BKA), does not require a prosthesis and has a lower energy expenditure.[9] However, TMAs are associated with significant failure or re-amputation rates of between 26% and 63%.[9,10] Although previous studies have attempted to identify the risk factors associated with failure of TMA, some are found to be conflicting. Many of the studies evaluating TMA were conducted in western populations. Hence, this study aims to evaluate the outcomes of TMA in the Asian population

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and identify risk factors associated with TMA failure.

Methods

Study cohort

A retrospective study was conducted in 147 patients with PAD who underwent TMA between 2008 and 2014 at a 1,500-bed university tertiary hospital. Patients whose surgery was performed for other reasons, such as trauma or malignancies, were excluded.

Management of PAD

A multi-disciplinary team headed by the vascular surgeons manages patients with PAD. Pre-operatively, vasculature was evaluated by ABI with toe pressures, either with arterial duplex imaging or computed tomography (CT) angiogram. Revascularisation modalities include both endovascular and open bypasses. For patients with foot sepsis or tissue loss, empirical antibiotics were carried out in accordance with the hospital's antibiogram and subsequently switched to targeted therapy according to cultures.

The decision for a TMA was made only if the patient did not have tissue loss proximal to the midfoot, had adequate vascularity to the infra-popliteal region and assessed to have ambulatory potential after amputation. Patients not fulfilling these criteria were offered a more proximal amputation, either below or above the level of the knee. We do not perform ankle disarticulation amputations in our institution for patients with PAD. Revascularisation was performed with either open (open bypass) or endovascular methods (percutaneous angioplasty). Revascularisation was offered to patients with toe pressures of <50 mmHg with the issue of tissue loss, or in selected cases with poor wound healing and severe disease shown on preoperative imaging. A consultant Interventional radiologist or vascular surgeon performed angioplasty. Moreover, TMAs were performed in a guillotine fashion, ensuring a complete debridement of non-viable tissue before leaving the wounds to heal via secondary intention. None of our study population had their TMA wounds closed primarily. Negative pressure wound therapy (NPWT) is applied to these wounds immediately patients are discharged. Home NPWT was also carried out for at least 2 to 6 weeks before an outpatient evaluation in the clinic. Split skin grafts are performed for granulating wounds to expedite healing. All amputations were performed by vascular surgeons.

Outcomes

The primary outcome of the study was the failure of an initial TMA, defined as patients required a subsequent BKA (trans-tibial amputation) because of the failure of wound healing. Secondary outcomes evaluated include a need for subsequent debridement or split skin grafting, post-operative complications (acute myocardial infarction, cerebral vascular accident, acute kidney injury, and nosocomial infections), 30-day re-admission rates and all-cause mortality. Multivariate analysis was used to identify the risk factors predicting the TMA failure.

In accordance with the Singapore Ministry of Health's guidelines, hypertension was defined as a blood pressure level ≥140/90, having diabetes at a 2-hour oral glucose tolerance test ≥11.1 mmol/L, and hyperlipidemia at a total cholesterol ≥6.2 mmol/L. End-stage renal failure was defined as patients were offered renal replacement therapy. Ischemic heart disease was recorded for patients who had a previous myocardial infarction or documented cardiac investigation revealing significant cardiac disease. Visual impairment was recorded for patients who had documented diabetic retinopathy in a follow-up.

Statistical Analysis

Descriptive statistics were used to evaluate demographics and provide the results of the present investigation. Percentages were used for categorical data and means with standard deviations (SD) for continuous data. Comparisons between groups for categorical data were carried out with the aid of chi-square tests while continuous data were done using Student's t-test. Univariate analysis was performed to identify factors associated with TMA's failure, using a cutoff p-value of 0.2. Moreover, we used multivariate logistic regression to identify independent risk factors associated with TMA failure. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated. All p-values <0.05 were considered statistically significant and p-values were two-tailed. SPSS 17.0 (Chicago, IL, USA) was used for the statistical analysis.

Results

A total of 147 patients underwent TMA during the study period (**Table 1**). The mean age was 65.9 (range 43–85). The majority were male (69%); and the racial distribution matched the local population with the majority being Chinese (69%). The majority of patients had significant co-morbidities, with 122 patients (85%) having an American Society of Anesthesiologist (ASA) status classification of 3 or 4. Although only 26% were smokers, the study population had a larger proportion of co-morbidities than the local population because of a higher incidence of smoking.[11] Type II DM and hypertension were present in 92% and 94% of patients, respectively, compared to only 11% and 24% in the general population. More than half (53%) of the patients with DM had the sub-optimal disease of a HbA1c level of >7%. More than two-thirds

Table 1 Univariate and multivariate analysis of factors predicting failure of TMA

TMA (n=147)	TMA failure (n=54, 37%)	TMA success (n=93, 63%)	Univariate p-value	Multivariate
Demographics				
Mean age (range)	65.1 (43–84)	66.4 (49–85)	0.467	
Male	34 (63%)	67 (72%)	0.252	
Ethnicity			0.723	
- Chinese	39 (72%)	63 (68%)		
- Malay	9 (17%)	17 (18%)		
- Indian	6 (11%)	11 (12%)		
- Others	0	2 (2%)		
Co-morbidities				
Smoker	15 (28%)	23 (25%)	0.244	
Diabetes	53 (98%)	82 (88%)	**0.033**	**0.032**
HbA1c >7%	31 (57%)	47 (51%)	0.576	
Hypertension	52 (96%)	86 (93%)	0.351	
Hyperlipidemia	49 (91%)	77 (83%)	0.184	0.236
Ischemic heart disease	23 (43%)	51 (55%)	0.152	0.131
Ejection fraction<55%	14 (26%)	27/93 (29%)	0.244	
ESRF	15 (28%)	22 (24%)	0.579	
Visual impairment	18 (33%)	33 (36%)	0.792	
Previous amputation	37 (69%)	64 (69%)	0.970	
ASA			0.633	
- 2	9 (17%)	13 (14%)		
- 3	41 (76%)	76 (82%)		
- 4	4 (7%)	4 (4%)		
Clinical presentation				
Ulcer	13 (24%)	20 (22%)	0.719	
Wet gangrene	35 (65%)	79 (85%)	0.228	
Dry gangrene	17 (32%)	22 (24%)	0.300	
Wound culture				
Positive vs. negative	41 (76%)	60 (65%)	0.150	0.343
>1 organism	19 (35%)	23 (25%)	0.255	
MRSA	7 (13%)	7 (8%)	0.261	
Pseudomonas	11 (20%)	12 (13%)	0.254	
Toe Pressure <50 mmHg	42 (78%)	75 (81%)	0.173	
Below-knee patency post-revascularisation				
ATA	22 (41%)	43 (46%)	0.366	
PTA	18 (33%)	40 (43%)	0.160	0.106
Peroneal	29 (54%)	49 (53%)	0.883	
Plantar arch	17 (32%)	27 (29%)	0.874	
Below-knee patency post-revascularisation				
3-vessels	7 (13%)	16 (17%)	0.485	
2-vessels	15 (28%)	27 (29%)	0.936	
1-vessel	22 (40.7%)	31 (33.3%)	0.773	

of these patients (69%) had a previous minor or a major lower limb amputation.

A large number of patients developed wet gangrene (71%). Wound cultures were positive in 69% of the patients, with 29% having multiple bacteria isolated. Preoperative toe pressures were measured, with 117 patients (79.6%) having toe pressures of <50 mmHg. Only two

Table 2 Outcomes of TMA

Outcome	Results (n=147)
Further amputation	54 (36.7%)
Debridement	35 (23.8%)
Split skin graft	11 (7.5%)

Table 3 Complications after TMA

TMA (n=147)	TMA failure (n=54, 37%)	TMA success (n=93, 63%)	Univariate p-value
Acute myocardial infarction	10 (19%)	8 (9%)	0.077
Cerebrovascular accident	3 (6%)	5 (5%)	0.963
Acute kidney injury	7 (13%)	6 (7%)	0.180
Nosocomial infection	15 (28%)	12 (13%)	**0.025**
30-Day re-admission	17 (32%)	10 (11%)	**0.002**
All-cause mortality	9 (17%)	12 (12.9%)	0.660
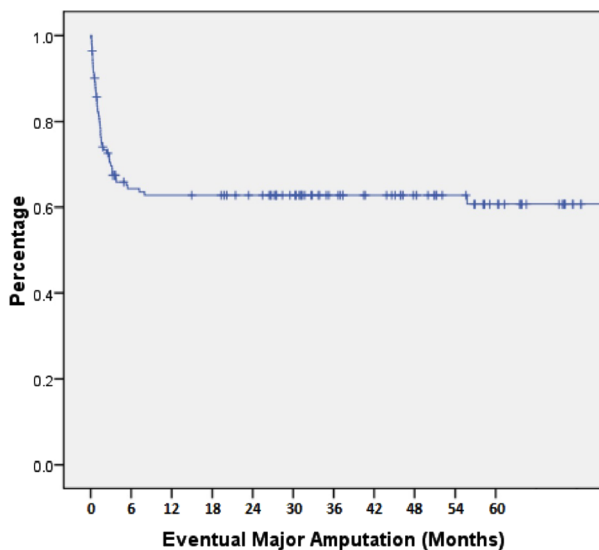
Number at Risk (Months)	0	6	12	18	24	30	36	42	48	54	60
	147	84	82	80	80	80	79	79	79	79	79

Fig. 1 Overall Limb Salvage. Kaplan–Meier survival curve indicating limb loss for all patients included. Major amputation rates at 6-months, 12-months, 24-months, 36-months, 48-months, and 60-months were 35.4%, 36.7%, 36.7%, 37.4%, 37.4%, and 37.4% respectively.

Table 4 Causes of death (n=21)

Urosepsis	1 (4.8%)
Lower limb gangrene	4 (19%)
Pneumonia	4 (19%)
End-stage renal failure	2 (9.5%)
Bleeding gastrointestinal tract	2 (9.5%)
Cerebrovascular accident	2 (9.5%)
Acute myocardial infarction	4 (19%)

patients had an open bypass procedure, while the rest of the revascularisations were performed via percutaneous angioplasty. At post-revascularisation, all patients had an in-line flow to the foot, with at least a single-vessel below-knee run-off. Anterior tibial artery (ATA), posterior tibial artery (PTA), peroneal artery, and plantar arch patency were 44%, 40%, 53%, and 30%, respectively. Patients with below-knee 3-vessels, 2-vessels and 1-vessel run-off were 16%, 29%, and 57%, respectively.

In terms of TMA outcomes, 93 patients (63%) had a complete healing of TMA. 35 patients (24%) required further surgical debridement while 11 patients (8%) required interval split skin grafting after a period of NPWT (**Table 2**). The mean time for patients to receive a skin graft was 62 days. The need for surgical debridement was not predictive of TMA failure (p=0.096). However, 54 patients (37%) had poor TMA wound healing, which even-

tually required a BKA. Multivariate analysis showed that diabetes was the only independent predictor of TMA failure (OR 7.11, p=0.064). Patients with TMA failure were at an increased risk of developing nosocomial infections (p=0.025) and have a higher re-admission rate within 30 days (p=0.002) (**Table 3**). Eventual major amputation rates at 6-months, 12-months, 24-months, 36-months, 48-months and 60-months were 35.4%, 36.7%, 36.7%, 37.4%, 37.4%, and 37.4%, respectively (**Fig. 1**). All-cause mortality rates at 12-months, 24-months, 36-months, 48-months, and 60-months were 12.2%, 14.3%, 14.3%, 14.3%, and 14.3%, respectively. Only four patients died from sepsis resulting from lower limb gangrene, while other patients passed away from the complications relating to diabetes and chronic diseases (**Table 4**).

Discussion

McKittrick was the first researcher to describe TMA in 1949 who reported it as a limb salvage procedure for diabetic patients.[12] It was traditionally described as an amputation procedure, including the metatarsal plantar mobilized for flap coverage. Arterial reconstruction and careful selection of patients showed decent healing rates of up to 46% after 5 years.[13] However, there are still a large number of patients who suffered from skin breakdowns after TMA,[14] leading to over closing of a skin flap on the wound. In this wise, NPWT has been shown to significantly improve wound healing rates.[15] Our institution preference is to leave the wound open after amputation and initiate NPWT. Most patients had significant gangrene, limiting the availability of healthy skin for flap closure. The primary closure also results in significant wound tension. In addition, most of the patients were diabetic and

at higher risks of wound infections.[16] Our institution has since adopted this procedure, preferring to use NPWT to encourage granulation before considering skin grafting for selected patients.

More proximal amputations, such as a BKA or above-knee amputation (AKA), usually have a higher healing rate.[9] However, the drawback is the higher energy expenditure required for ambulating with a subsequent prosthesis. BKA is associated with an acceptable failure rate of 9% and a risk of failure in patients with end-stage renal failure (ESRF) or previously non-ambulant.[17] It is also important to note that these patients have a higher mortality rate, with almost two-thirds of amputees having a contralateral amputation afterward.[18]

The success TMA's rates reported in the literature are from 27% to 63%.[9,10,19–22] It is important to identify factors predisposing to TMA's failure to reduce the rate of re-admissions that add to both healthcare burden and patient morbidity. Several studies have suggested variable risk factors associated with failure of amputations, which include sepsis, emergency surgery, ESRF, trainee participation, high body mass index (BMI), and long operating duration.[10,19,23] However, these are not consistent among various studies, which have been mostly performed in western populations. Thus, one of the objectives of our study was to evaluate TMAs in an Asian population.

Identifying the risk factors for the failure of TMAs is a key interest in addressing the significant re-operation rates. However, the risk factors identified by previous studies are conflicting.[20] While critical limb ischemia is clearly a risk factor,[9] attempts at using ABI or angiography results to predict TMA's failure have not been accurate.[24] End-stage renal failure is frequently associated with TMA's failure in literature,[21] however, it was not found to be significant in this study. Poor glycemic control in diabetic patients has also been shown to be associated with poorer outcomes after amputations, hence prompting some authors to advocate avoiding elective amputations in patients with a HbA1c of over 8%.[25] Although diabetic control was not identified as a significant risk factor in this study, the presence of type II DM was clearly associated with a significantly higher risk of TMA failure.

The incidence of diabetes in Asia is on the rise and it is estimated that more than 60% of world diabetic patients are in Asia.[26] Moreover, the prevalence of diabetes is approximately 11.3% and expected to increase.[11] However, we noted a considerably different prevalence risk factors are identified in this study population versus the average western population with peripheral arterial disease. Almost all our patients had diabetes, and only one-quarter of them were smokers. These differences are important, given that diabetes itself has been shown to contribute to poorer outcomes in patients with PAD.[8]

Ensuring adequate vascularity is a key important factor for TMAs. Typically, TMA healing rates were shown to improve from 62% to 83% after surgical bypass.[27] Preoperative and intra-operative assessments are vital in deciding if a TMA is suitable. A retrospective analysis of TMA revealed a 92% healing rate if patients had all of these 3 factors: minimum ABI of 0.45 in non-diabetics and 0.5 in diabetics, blood total lymphocyte count of $>1.5\times10^3/\mu L$ and serum albumin $\geq3\,g/dL$.[28] Other studies suggest other modalities for wound healing, such as transcutaneous oxygen pressure ($TcPO_2$),[29] where revascularisation is recommended if the $TcPO_2$ is $<30\,mmHg$.[30]

In the current study, all patients received at least one vascular imaging modality (mostly arterial duplex ultrasounds) before amputation. This enables clinicians to offer revascularisation pre-operatively to enhance wound healing rates. Most of the patients underwent percutaneous angioplasty performed by both vascular surgeons and Interventional radiologists at this institution. Analyses of the vascular patency of the affected limbs revealed a trend toward a higher failure rate in patients with the more significant infra-popliteal disease, but did not reach statistical significance. We also analyzed the number of occluded infra-popliteal arteries, but this also did not reveal any significant difference. The pedal arch patency is known to affect wound healing rates,[31] but this was again not significantly different between both groups. Toe pressures were also analyzed in both groups, with a cutoff of $<50\,mmHg$, which was generally indicative of poorer outcomes. This is in accordance with the International Working Group for the Diabetic Foot (IWGDF), guidelines for the management of diabetic foot ulcers.[32] However, this also did not show any statistical difference.

The risks and benefits of TMA in diabetic limb salvage should be individualized for each patient. TMA should still be considered as it results in ultimately good function and has a reasonable success rate of 63% according to our results. However, the patient should be well counseled on the risks of failure, and revascularisation should be performed to improve vascularity. TMA should also only be offered to patients who will enjoy functional benefits from limb salvage.

This study has several limitations. Given its retrospective nature, we were unable to determine how patients were selected for TMA. This is important for the decision for TMA encompasses many different factors, including clinical, biochemical, and social factors. Although data were collected over a 7-year period, our sample size is still relatively small. This could lead to insufficient statistical power to identify important associations. Despite these limitations, this study still serves as an important TMA's review in an Asian context. Further studies will be required to identify the risk factors to improve our selection

of patients undergoing TMA.

Conclusion

The success rate for PAD limb salvage TMA was 63% and the presence of diabetes is an independent predictor of TMA failure. As patients with TMA failure were at increased risks of nosocomial infections and 30-day re-admissions, the risks and benefits of TMA for diabetic foot limb salvage must be individualized for each patient.

Disclosure Statement

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Author Contributions

Study conception: ZJL, MNAT
Data collection: MNAT, SHL, RMT
Analysis: MNAT, SHL, ZJL
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