

# Predictors of Healing and Functional Outcome Following Transmetatarsal Amputations

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**Objectives:** To evaluate factors that predict healing and to assess functional outcome and survival following transmetatarsal amputations (TMAs) for forefoot gangrene.

**Design:** Retrospective case-control study.

**Setting:** University hospital.

**Patients:** All patients undergoing TMA from January 1, 2004, through December 31, 2010.

**Intervention:** Transmetatarsal amputations performed in all patients.

**Main Outcome Measures:** Transmetatarsal amputation healing, ambulation, living status, and survival. Demographic characteristics, preoperative vascular status, and perioperative variables were analyzed as predictor variables. Univariate and multivariate analyses were performed to determine predictors of healing and survival.

**Results:** Sixty-two TMAs were performed in 57 patients. Healing occurred in 33 TMAs (53%), with 22 TMAs

(35%) in patients who proceeded to below-knee amputation and 7 TMAs (11%) in patients who died without healing. No demographic or perioperative variables significantly predicted healing. Independent ambulation was achieved in 24 patients with healed TMAs (73%) but in only 4 patients with nonhealed TMAs (14%) ( $P < .001$ ). Mean survival was 16.5 months (range, 0-94 months), with no difference between patients with healed and those with nonhealed TMA. Significant predictors of mortality were dialysis-dependent renal failure (odds ratio, 4.85; 95% confidence interval, 1.01-23.30) ( $P = .047$ ), non-independent living (17.80; 3.03-104.80) ( $P = .001$ ), and need for preoperative revascularization (4.80; 1.24-18.50) ( $P = .02$ ).

**Conclusions:** Transmetatarsal amputations have low healing rates, and patient demographic characteristics and preoperative assessment do not help predict healing. Transmetatarsal amputation healing, however, significantly predicts subsequent ambulatory status and should be pursued in patients with good rehabilitation potential.

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**F**OR MANY PATIENTS WITH MULTIPLE toe or distal foot gangrene, a transmetatarsal amputation (TMA) is the last hope for partial foot salvage. Preservation of a sensate heal is desirable for maintaining ambulatory function. However, wound healing of TMA is frequently a major challenge. Wound healing rates from multiple series<sup>1-7</sup> range from approximately 40% to 70%. Nonhealing of TMA inevitably leads to multiple operations and hospitalizations, ultimately resulting in a more proximal, frequently transtibial, amputation.

Although transtibial amputations heal more reliably than TMAs, patients are often resistant to this procedure, and subsequent ambulation with a prosthesis is often more difficult than ambulation on the native heal and forefoot. Given the difficulty in healing of TMA, however, it would be desirable to predict which patients are

less likely to heal and to possibly avoid the prolonged periods of medical care in these patients.

## See Invited Critique at end of article

Typically, the judgment of an experienced physician is one of the best indicators of subsequent healing. Other adjunctive measures, such as ankle brachial indices, toe pressures,<sup>8</sup> laser Doppler skin perfusion pressures,<sup>9</sup> angiography,<sup>3</sup> and Doppler assessment of foot vasculature,<sup>10</sup> are occasionally used to assist in this decision. In our practice, we have used a variety of tests to help determine optimal amputation levels, most recently, skin perfusion pressures. Here, we review our experience with TMA healing and examine factors that might help predict amputation healing.

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**Table 1. Demographic Data for Patient Cohort<sup>a</sup>**

Factor	Value
Age, mean (SD), y	60.7 (13.4)
Male sex	60
BMI, mean (SD) <sup>b</sup>	27.6 (8.5)
Active smoker	18
Hypertension	63
Coronary artery disease	37
Congestive heart failure	32
COPD	21
Diabetes mellitus	79
Renal insufficiency	21
Renal failure	31
Hypercholesterolemia	44

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease.

<sup>a</sup>Data are given as percentage of patients unless otherwise specified.

<sup>b</sup>Calculated as weight in kilograms divided by height in meters squared.

## METHODS

### PATIENTS

The study was approved by the institutional review board at Oregon Health & Science University (Portland). The study was a retrospective analysis of outcomes of TMA performed in the Division of Vascular Surgery at Oregon Health & Science University from January 1, 2004, through December 31, 2010. Consecutive patients with a history of TMA were included, regardless of outcome.

### DEMOGRAPHIC CHARACTERISTICS

Each patient's age, sex, and body mass index were documented. In addition, the following factors were recorded: current smoking status and documented history of cardiovascular disease, pulmonary disease, diabetes mellitus, renal insufficiency or failure (with renal insufficiency defined as a blood creatinine level >1.5 mg/dL [to convert to micromoles per liter, multiply by 88.4]) on 3 separate occasions surrounding the operation and with renal failure defined by need for dialysis), hypertension, and hypercholesterolemia. All patients with hypercholesterolemia were receiving statin therapy. All patients were receiving antiplatelet therapy, either aspirin, clopidogrel bisulfate, or both.

### PERIOPERATIVE AND POSTOPERATIVE DATA

Preoperative data evaluated included ankle brachial index, toe brachial index, and skin perfusion pressure. Preoperative cardiac evaluation was performed in patients with recent (within 6 months) history of myocardial infarction, unstable angina, electrocardiographic changes, or poor functional status (American Society of Anesthesiology class III or IV). Revascularization, either endovascular or surgical, before amputation was performed at the discretion of the surgeon if perfusion for wound healing was believed to be inadequate. Transmetatarsal amputation was then performed later as a second-stage procedure. Likewise, amputation without prior revascularization was at the discretion of the surgeon. Transmetatarsal amputations were performed using standard published techniques.<sup>11</sup> In the absence of gross infection, wounds were primarily closed, whereas grossly infected wounds were left open at the initial operation for delayed primary or secondary closure. Casting was not performed following TMA, but strict non-weight-bearing status for 1 month was encouraged.

Both intraoperative and postoperative factors that are believed to potentially affect wound healing were assessed. Intraoperatively, blood pressure and temperature were recorded. In addition, 24-hour postoperative data of blood pressure, temperature (high and low), blood glucose (high, low, and mean), and oxygen saturation were recorded. Additional postoperative factors evaluated were primary wound closure, time to secondary wound closure, time to below-knee amputation if performed, total number of operations, postoperative ambulatory status, living status (independent or nonindependent), limb salvage, and survival. Postoperative data were retrieved from the electronic medical records (Epic; Epic Systems Corporation, Madison, Wisconsin), and mortality data were obtained from the electronic medical record or Social Security Death Index. Data were recorded in a computerized database (Excel; Microsoft Corporation, Redmond, Washington).

## STATISTICAL ANALYSIS

All data were analyzed using SPSS, version 19.0 (SPSS, Inc, Chicago, Illinois). Both univariate and multivariate analyses were conducted. Continuous variables were compared using the *t* test. Categorical variables were compared using the Pearson  $\chi^2$  test or Fisher exact test, as appropriate. Stepwise logistic regression analysis was performed to assess factors associated with TMA healing. Limb salvage and survival were calculated with Kaplan-Meier analysis. The level of significance was set at  $P < .05$ .

## RESULTS

During the study period, 62 TMAs were performed in 57 patients. Demographic data on the study cohort are listed in **Table 1**. In the study population, 79% of the patients had diabetes and 31% had dialysis-dependent renal failure. Thirty-three TMAs (53%) healed. Twenty-two TMAs (35%) resulted in below-knee amputation. In 7 TMAs (11%), the patient died without complete TMA healing. Primary closure was performed in 45 TMAs (73%), whereas 17 TMAs (27%) were left open for delayed primary or secondary closure. Eleven of 17 patients (65%) whose wounds were left open ultimately healed, with a mean healing time of 5.2 months (range, 1-36 months). There was no difference in wound healing between primary and delayed primary or secondary closure ( $P = .39$ ). In 36 TMAs (58%), the patients underwent either surgical or endovascular revascularization beforehand, whereas in 26 TMAs (42%), the patients were either believed to be adequately perfused or did not have revascularization options. At the time of amputation, 35 patients had measurable ankle brachial indices with a mean (SD) of 0.96 (0.18), whereas 27 had noncompressible ankle brachial indices.

The effects of demographic factors on TMA healing are listed in **Table 2**. There were no significant demographic differences between healers and nonhealers, although there was a trend toward decreased healing in patients with renal failure, chronic obstructive pulmonary disease, and cardiac disease. Other factors, including a history of diabetes, did not influence TMA healing.

Skin perfusion pressure was measured with laser Doppler in 23 patients. Measurement of skin perfusion pressures at the transmetatarsal and ankle levels did not predict subsequent TMA healing. Mean (SD) skin perfusion pressures at the transmetatarsal level were 17.9

**Table 2. Demographic Data Associated With Healed and Nonhealed TMAs<sup>a</sup>**

Factor	Healed TMAs (n=33)	Nonhealed TMAs (n=29)	P Value
Age, mean (SD), y	62.1 (11.7)	59.0 (15.3)	.38
Male sex	64	55	.50
BMI, mean (SD) <sup>b</sup>	27.6 (9.1)	27.6 (7.9)	.98
Noncompressible ABI	39	48	.48
Active smoking	21	14	.45
Hypertension	64	62	.90
CAD	30	45	.24
CHF	24	45	.15
COPD	12	31	.07
Diabetes mellitus	82	76	.57
Renal insufficiency	15	28	.23
Renal failure	21	41	.09
Hypercholesterolemia	42	45	.85
Primary closure	67	79	.27
Pre-TMA revascularization	58	59	.94

Abbreviations: ABI, ankle brachial index; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; TMA, transmetatarsal amputation.

<sup>a</sup>Data are given as percentage of patients unless otherwise specified.

<sup>b</sup>Calculated as weight in kilograms divided by height in meters squared.

(15.3) mm Hg in nonhealers and 26.9(24.3) mm Hg in healers ( $P=.32$ ) and at the ankle level were 44.4(18.4) mm Hg in nonhealers and 40.8(29.7) mm Hg in healers ( $P=.76$ ). Transcutaneous oxygen levels and toe pressures were infrequently measured and, therefore, not further analyzed.

Intraoperative and perioperative factors evaluated are presented in **Table 3**. No intraoperative data (systolic blood pressure and temperature) were predictive of subsequent healing. These parameters measured during the first 24 hours after operation likewise did not predict healing. On univariate analysis, patients with healed TMA had higher glucose levels (mean and high) than did nonhealers. In the multivariate model, no demographic or perioperative factors were predictive of TMA healing (data not shown).

The mean survival of the entire patient cohort was 16.5 months (range, 0-94 months). Mean survival did not differ between patients with and those without TMA healing (15.1 [16.4] vs 18.0 [18.8] months;  $P=.52$ ). Three patients (5%) died within 1 month of surgery: 1 of myocardial infarction, 1 of sepsis and multisystem organ failure, and 1 of undetermined cause (patient was in a skilled nursing facility). Survival at 12, 24, and 36 months for the entire group was 67%, 52%, and 35%, respectively. There was no difference in survival in patients with healed vs nonhealed TMA at the same times (healed: 64%, 45%, 37%; nonhealed: 75%, 59%, 33%;  $P=.90$ ) (**Figure**). On univariate analysis, significant predictors of mortality included renal failure (74% mortality in patients with renal failure vs 40% in patients without renal failure;  $P=.03$ ), nonambulation (62% vs 36%;  $P=.04$ ), nonindependent living (79% vs 21%;  $P<.001$ ), and pre-TMA revascularization (64% vs 31%;  $P=.01$ ).

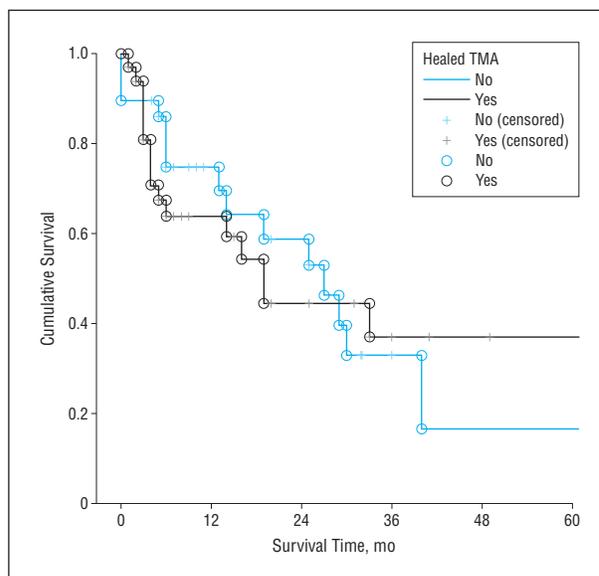
Multivariate predictors of death included renal failure (odds ratio, 4.85; 95% confidence interval, 1.01-

**Table 3. Intraoperative and Postoperative Data Associated With Healed and Nonhealed TMAs**

Factor	Mean (SD)		P Value
	Healed TMAs (n=33)	Nonhealed TMAs (n=29)	
Intraop temperature, °C	36.7 (0.3)	36.8 (0.6)	.40
Intraop SBP, mm Hg			
Mean	119 (20)	119 (16)	.91
Low	100 (20)	92 (16)	.16
Postop oxygen saturation, %	97.5 (1.6)	97.6 (1.7)	.77
Postop temp, °C			
Mean	36.8 (0.4)	36.7 (0.3)	.33
Low	36.3 (0.4)	36.1 (0.4)	.18
Postop glucose, mg/dL			
High	236 (131)	150 (74)	.008
Mean	183 (85)	132 (61)	.03
Low	134 (68)	115 (52)	.29
Postop SBP, mm Hg			
Mean	128 (24)	127 (20)	.83
Low	110 (23)	106 (25)	.65

Abbreviations: intraop, intraoperative; postop, postoperative; SBP, systolic blood pressure; TMA, transmetatarsal amputation.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.



**Figure.** Kaplan-Meier curve demonstrating survival of patients with healed and nonhealed transmetatarsal amputations (TMAs). *Censoring* refers to patients who are not followed up beyond the indicated time either because they were lost to follow-up or they are still being followed up but not beyond the indicated time.

23.30) ( $P=.047$ ), nonindependent living (17.80; 3.03-104.80) ( $P=.001$ ), and need for preoperative revascularization (4.80; 1.24-18.50) ( $P=.02$ ).

The mean amputation-free survival for the entire patient cohort was 8.1 months. Twenty-two of 29 patients with nonhealing TMA underwent below-knee amputation within 4 months of the TMA surgery, with no further amputations after 4 months. The remaining 7 patients died without TMA healing. Nonhealers underwent

a mean (SD) of 4.0 (1.8) operations from the time of their initial operation to either below-knee amputation or death. None of the 32 patients with healed TMA required further amputation or operations.

At the time of last follow-up, independent ambulation had been achieved in 24 of 33 patients with healed TMA (73%) but in only 4 of 29 patients with unhealed TMA (14%) ( $P < .001$ ). Independent living status was less affected by TMA healing. Twenty of 33 patients with healed TMA (61%) and 14 of 29 patients with unhealed TMA (48%) were living independently ( $P = .33$ ).

## COMMENT

Transmetatarsal amputation was first described as a method of partial foot preservation by McKittrick et al<sup>12</sup> in 1949. The present findings support those of prior studies showing suboptimal rates of healing of TMAs. Our TMA healing rate was 53%, which is consistent with data from multiple studies.<sup>1-7</sup> Unfortunately, no preoperative measures were able to accurately predict which patients would go on to heal their amputations, so clinical judgment still remains an important factor in deciding who should be offered this operation.

Preoperative assessment of arterial perfusion is typically pursued in patients with critical limb ischemia. In patients with forefoot gangrene, attempts were made to optimize arterial perfusion to the affected extremity with revascularization, either open or endovascular, when possible. Sheahan et al<sup>4</sup> found that a revascularization procedure performed subsequent to partial foot amputation was a predictor of subsequent limb loss and advocated early revascularization to optimize amputation healing. In the current series, patients undergoing TMA following revascularization had healing rates no different from those of patients who underwent amputation without revascularization. This may still indicate a delay in revascularization, because patients presented for revascularization with significant forefoot gangrene. Healing rates would likely be improved if patients were referred with less severe tissue loss. In addition, it is reasonable to surmise that revascularization before amputation did allow healing for some patients who might have gone directly to transtibial amputation if revascularization had not been performed.

More than half of the patients in this series had non-compressible ankle brachial indices, which is typical of a population in which a high percentage have diabetes and renal failure. Toe pressures were infrequently obtained because of the nature of the extensive forefoot gangrene. In the later years of the series, we typically performed assessment of skin perfusion pressure with laser Doppler to assess amputation healing potential. Others have found a skin perfusion pressure of more than 30 mm Hg to predict wound healing, particularly in more proximal limb amputations.<sup>9</sup> In this study, skin perfusion pressures did not predict ulcer healing, which likely indicates that arterial perfusion, while important, is not the only predictor of wound healing.

The findings regarding the effects of perioperative glycemic control on wound healing were somewhat paradoxical in this study. The cohort of patients with

healed TMAs had a higher mean glucose level in the first 24 hours after surgery, compared with the level in the group that did not heal, which was significant in univariate although not in multivariate analysis. Others have shown that hyperglycemia is a risk factor for poor wound healing in patients with diabetic foot ulcers<sup>13</sup> and that patients with a hemoglobin A<sub>1c</sub> level higher than 8% experience worse healing of TMA.<sup>14</sup> In our hospital, perioperative blood glucose levels are tightly controlled with the frequent use of insulin drips, such that hyperglycemic episodes are rare. One could hypothesize that the data indicate that hypoglycemic episodes are equally as disadvantageous in promoting wound healing as hyperglycemic episodes.

With such poor healing rates and survival, it is valid to question the wisdom of proceeding with TMA. Patients with dialysis-dependent renal failure in particular had poor wound healing and survival, as has been demonstrated by others.<sup>15</sup> Clearly, patient choice becomes an important factor, because patients in general wish to preserve as much of their limb as possible. Below-knee amputation is still a stigmatized procedure that patients will most likely defer as long as possible and at all reasonable cost. However, this and several similar studies demonstrate the importance of tempering expectations. Patients need to be aware of the relatively low likelihood of the success of this operation. Although this awareness is not likely to dissuade patients from pursuing it, at least patients will be informed of the tenuous nature of limb salvage in their particular situation. It is human nature to believe that bad outcomes will happen to someone else and not them, but armed with the knowledge that their operation has a relatively low likelihood of success, patients may be more likely to be compliant with the proscribed post-operative care recommendations, not the least of which is maintaining a non-weight-bearing status until the amputation site has healed. Although this study was not designed to evaluate patient compliance as a variable in amputation healing, we (and likely every surgeon) can anecdotally recall patients in whom seemingly well-healing amputation sites failed to heal and resulted in more proximal amputations because of trauma to the amputation site secondary to patient noncompliance.

This study clearly demonstrates superior functional status in patients in whom TMA healed, with significantly improved ambulatory and independent living status. The poor ambulatory performance of atherosclerotic patients with transtibial amputations is well documented.<sup>16</sup> Therefore, despite the accepted lower healing rates, it is reasonable to pursue TMA in patients with a higher likelihood of continued ambulation. It is often difficult to determine this preoperatively, because most patients express a wish to walk again. However, in patients in whom ambulation is clearly not a reasonable future goal, TMA is a suboptimal option because of its low healing rate and the need for additional operations and hospitalizations.

This study has several limitations, including its retrospective nature and relatively small numbers, which introduces the possibility of type II error. Because of the tertiary referral nature of our practice, many patients come from long distances, and long-term follow-up of this group is often difficult to obtain. Decisions regarding evalua-

tion and treatment of the patients were made by numerous physicians and were therefore not standardized, although in most cases the decision for amputation was by mutual agreement among the group.

In summary, TMA healing rates are poor, even with experienced surgeons and careful preoperative planning. Although we do not discourage careful planning, including the use of preoperative noninvasive vascular assessment, it is clear that no amount of planning will guarantee success. Patients should be made aware of the uncertainty of the procedure and the need for meticulous postoperative compliance to optimize the chances of procedural and postprocedural success. Because of the superior functional outcomes of patients with successful amputation healing, TMA should be offered to patients with favorable prospects for postoperative ambulation. In patients with poor rehabilitation prospects, TMA may lead to additional procedures and hospitalizations, and a more proximal amputation with a higher likelihood of healing may be preferable.

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## INVITED CRITIQUE

# The Elusive Search for Predictors of Healing Following Transmetatarsal Amputation

The role of the surgeon engaged in the treatment of patients with vascular disorders has less to do with eradication of disease and more to do with maintaining or improving quality of life for his or her patients. To that end, the goal of any limb-salvage surgery is to preserve preoperative ambulatory status. Multiple studies have demonstrated ambulation rates of less than 50% following below-knee amputation. On the contrary, a patient with a healed forefoot amputation has a high likelihood of ambulation because of the preserved mechanics of normal ambulation and the lack of need

for a prosthetic. In this well-written article by Landry and colleagues,<sup>1</sup> the group retrospectively analyzes their experience with 62 transmetatarsal amputations (TMAs) during a 6-year period, and their results validate the importance of the TMA because almost 75% of patients with healed TMA achieved ambulatory status. In addition, although not specifically addressed in the article, the time to ambulation in patients with successful TMA is generally a fraction of the time typically required for a patient with a below-knee amputation to complete the rehabilitation required to walk with a prosthetic.