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Reconstructive

Limb Salvage via Surgical Soft-tissue Reconstruction With Ovine Forestomach Matrix Grafts: A Prospective Study

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Background: Complex and chronic lower extremity defects present a surgical challenge and can progress to eventual amputation if closure is not achieved. In addition to morbidity and mortality, these defects have a significant impact on patient quality of life and represent a substantial cost burden to the healthcare system. Ovine forestomach matrix (OFM) grafts are an advanced tissue scaffold option to supplement the surgical reconstruction ladder and may augment limb preservation in cases of complex lower extremity defects.

Methods: A prospective observational study enrolled 130 complex lower extremity reconstructions that received OFM as part of surgical management. Granulation tissue formation, defect closure, and postoperative complications were assessed up to 1 year postoperatively to evaluate the outcome of OFM grafts for limb salvage via surgical reconstruction.

Results: Participant demographics and defect characteristics were reflective of a real-world inpatient population with complex and chronic defects. Despite complexity of the defects, no postoperative infections or major amputations were reported. The median time to complete granulation tissue coverage and fill was 30.0 days (95% confidence interval, 26.9–33.1) and the median time to complete defect closure was 127.0 days (95% confidence interval, 110.5–143.5). At 180 days, a 62% incidence of healing was achieved with a median product application of 1.0 (interquartile range, 1.0–1.0).

Conclusions: OFM-based grafts supported successful coverage of lower extremity defects in a real-world cohort with known risk-factors for amputation. Achieving successful closure with minimal complications, and often in a single application, suggests utility of OFM as a cost-effective adjunct in lower extremity reconstruction.
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INTRODUCTION

There is an increasing prevalence of chronic lower extremity wounds, including diabetic foot ulcers (DFU), venous leg ulcers, necrotizing soft-tissue infection, burns, and trauma.[1] These wounds are often managed to closure in outpatient settings using standard wound care. However, more severe defects may require aggressive surgical interventions as a means to prevent eventual lower extremity amputation (LEA).[2] If standard wound care or limb preservation fails, amputation becomes likely, especially impacting patients with multiple comorbidities who may not be optimal amputation candidates.[3]

Dermal substitutes, including decellularized extracellular matrices (dECM), and synthetic and biologic grafts have become increasingly common treatment options for surgical reconstruction of complex soft tissue defects.[4] Although there is a large body of published evidence describing the use of dermal substitutes in outpatient

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lower extremity wound care, there are fewer studies focused specifically on inpatient surgical reconstruction of complex lower extremity defects using these products.

Ovine forestomach matrix (OFM) is a well-studied dECM biomaterial available for both inpatient and outpatient soft tissue regeneration. OFM is a bioscaffold comprising the decellularized propria submucosa isolated from sheep forestomach ("rumen") tissue.[5] Preclinical studies have shown that OFM comprises naturally occurring ECM-associated proteins and proteoglycans critical to the wound healing cascade, promotes angiogenesis, and augments healthy granulation tissue formation.[5–7] OFM-based products seem to resist bacterial colonization, so they have found a place in reconstructing contaminated soft tissue defects.[8–11] The effectiveness of OFM in these contaminated defects may be attributable to the ability to rapidly form well-vascularized tissue[12] and modulate tissue proteases that prolong inflammation[13] or naturally occurring bacteriostatic proteins that are known to exist in the ECM.[14]

In the outpatient setting, OFM-based products have been shown to be effective in treating lower extremity wounds including DFU,[15] venous leg ulcers,[16] pressure injuries, and traumatic wounds.[17–19] In surgical reconstruction, these products can be used to regenerate tissue coverage over exposed structures and fill soft-tissue defects,[10,20] and can be used as part of a staged reconstruction[20,21] or implanted to fill subcutaneous tissue voids.[22,23] In a prior multicenter retrospective study, Bosque et al[24] reported the surgical reconstruction of 50 complex lower-extremity soft-tissue defects with OFM-based grafts, suggesting a place for OFM-based grafts in the reconstruction of complex lower extremity defects.

In the current study, we report results from a prospective, single-arm, observational study evaluating the use of OFM grafts in the surgical reconstruction of complex lower extremity defects deemed high-risk for amputation. The aim of this study was to prospectively validate the real-world outcomes of OFM grafts in the surgical reconstruction of hard-to-heal lower limb defects that had failed standard of care wound management and that may have otherwise progressed to eventual amputation.

Takeaways

Question: Do ovine forestomach matrix (OFM) grafts offer a safe and cost-effective option for the surgical reconstruction of complex lower extremity defects as part of limb salvage?

Findings: OFM grafts were used in 130 complex defects deemed high risk for amputation with a median time to closure of 127 days and 0 instances of infection or major amputation. Soft-tissue coverage and fill, often involving exposed structures, was achieved with a single-graft application.

Meaning: This large prospective study has shown that OFM grafts are a safe and reliable component of the surgical reconstruction algorithm for lower extremity defects that may otherwise proceed to amputation.

METHODS

General

This study represents a subgroup analysis from an institutional review board (IRB)-approved prospective, single-arm, multicenter, observational registry (NCT05243966) evaluating the safety and efficacy of OFM grafts in surgical reconstruction. The study was approved by an independent central IRB (Advarra Institutional Review Board Services, MD) and all patients provided written informed consent for the collection of de-identified data. The current analysis included all sequential participants enrolled in NCT05243966 who had undergone inpatient surgical reconstruction of complex lower extremity soft-tissue defects during the period of May 2022 to April 2023 from a single site. Inclusion criteria included patients (≥18 years old) who had received an OFM graft and/or OFM particulate (Myriad Matrix Soft Tissue Bioscaffold/Myriad Morcells, Aroa Biosurgery Ltd, New Zealand) as part of their inpatient surgical reconstruction (Table 1). No participants who received the OFM graft as part of their surgical management were excluded from the analysis. Reflecting the real-world population of this study, all participants enrolled in the study were included in the analysis regardless of postoperative protocol deviations or follow-up adherence (intent to treat population). The primary study outcome was the nature, frequency, and severity of treatment emergent adverse events. Secondary endpoints included postoperative complications (eg, infection, pain, and recurrence), time to granulation tissue coverage, and time to defect closure.

Data Recording

All data were recorded prospectively using a mobile electronic case report form (Tissue Analytics, Net Health,

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Willing and able to provide written informed consent and to comply with the requirements of clinical investigational plan • Male or female patients aged 18 y or older • Patients where OFM graft and/or particulate were used as part of their soft-tissue reconstruction procedure • Subjects that are willing and able to comply with all aspects of the treatment and evaluation schedule	• Patients with known sensitivity to ovine (sheep)-derived material • Patients with full-thickness ("third-degree") burns • Patients with wounds with uncontrolled clinical infection (CDC Contamination Grade = 4) • Any medical condition or serious intercurrent illness that, in the opinion of the investigator, may make it undesirable for the patient to participate in the study • Patient is currently participating or has participated in another clinical study within past 30 days before enrollment • Pregnant or lactating women • Any subject who, at the discretion of the investigator, is not suitable for inclusion in the study

Inc.). Patient demographics and significant baseline comorbidities were recorded on presentation, along with defect etiology. Amputation risk indices for each participant were determined according to Lin et al,[25] with modifications. (**See table, Supplemental Digital Content 1**, which displays predictors for LEA, **http://links.lww.com/PRSGO/D721**) Defect size (cm^2) was measured post-debridement at the initial surgery and follow-up visits using telemetry (Tissue Analytics). The presence of exposed structures (eg, tendon, bone) and baseline characteristics (eg, defect size, Centers for Disease Control and Prevention [CDC] grade) were assessed at the initial surgery. Granulation tissue formation was subjectively assessed by the attending surgeon at each visit and evaluated based on coverage of exposed structures and/or depth of fill. The endpoint, time (days) to granulation tissue coverage, reflected the elapsed time from OFM graft placement to when the defect bed was judged sufficiently granulated by the attending surgeon. The defect was judged closed by the attending surgeon based on the absence of drainage and complete epithelial coverage. Closure was further verified using the wound telemetry function of the electronic case report form (Tissue Analytics). In the event of disagreement between the surgeon and the automated wound telemetry, the second surgeon validated the outcome. Preoperative and postoperative patient pain and scar outcome was assessed. (**See table, Supplemental Digital Content 2**, which displays Vancouver Scar Scale assessment, **http://links.lww.com/PRSGO/D722**.) Descriptive statistics were computed using GraphPad Prism (version 10.1.2, GraphPad Software, LLC). Kaplan-Meier (KM) survival analysis was conducted using SPSS (v26).

Surgical Reconstruction

OFM, in either graft or morselized ("particulate" or "powder") form, was used in accordance with the manufacturer's instructions for use. The defects thoroughly debrided under general anesthesia or monitored anesthesia care to remove all necrotic tissue and lavaged with sterile saline. OFM graft (3- or 5-layer), morselized OFM, or a combination thereof was applied either topically for dermal regeneration or implanted before closure via primary intention (Fig. 1). In both instances, OFM grafts were rehydrated (<5 minutes, sterile saline); trimmed to size as required; and fixed to the defect edges, or subcutaneous tissues in instances of undermined tissue, with absorbable Vicryl (polyglactin 910). (**See table, Supplemental Digital Content 3**, which displays intraoperative placement of OFM grafts and defect healing, **http://links.lww.com/PRSGO/D723**.) If OFM particulate was used in combination with OFM graft, particulate was applied over the graft. The defects were dressed using a nonadherent contact layer (Adaptic, 3M/KCI, St. Paul, MN), 4 × 4 inch gauze, gauze roll, and compressive wrap. At dressing change, wounds were assessed for integration of the OFM grafts, granulation tissue formation, closure, and any complications. Initial follow-up

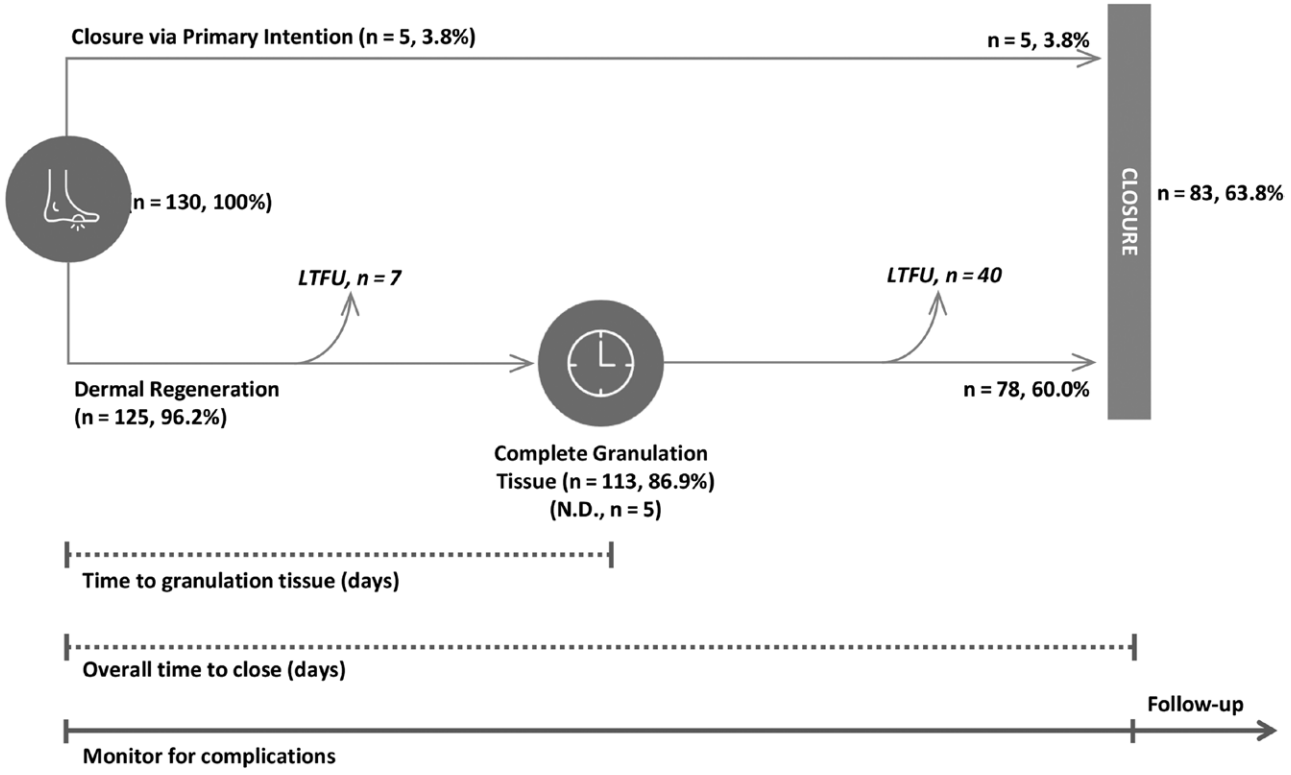

Fig. 1. Study population included n = 130 complex lower extremity defects reconstructed either via primary intention (n = 5), or dermal regeneration (n = 125). LTFU, lost to follow-up.

was conducted approximately weekly, with a transition to 3-month follow-up intervals after complete closure was achieved (**Supplemental Digital Content 3**, **http://links.lww.com/PRSGO/D723**).

Literature Review

A literature review was undertaken according to Supplemental Digital Content 4. (**See table, Supplemental Digital Content 4**, which displays literature synthesis protocol. **http://links.lww.com/PRSGO/D724**.) Inclusion was limited to articles that described inpatient surgical reconstruction of complex lower extremity soft tissue defects. Acute traumatic lower extremity reconstructions and outpatient lower extremity wound care were specifically excluded.

RESULTS

Patient Demographics

A total of 120 consecutive participants (Table 2) were included in the study, who met both inclusion and exclusion criteria. The mean participant age was 62.5 ± 14.1 years, with 85 men (70.8%) and 35 women (29.2%). The median body mass index (BMI) was 29.3 kg/m^2 (interquartile range [IQR], 26.4–35.7 kg/m^2), and the prevalence of tobacco use was 27.5% (n = 33 of 20). Of the 109 (90.8%) participants diagnosed with diabetes mellitus, 70.8% (n = 85 of 120) had uncontrolled disease. Across all participants, 95.8% (n = 105 of 120) had at least 1 risk-factor for LEA (**Supplemental Digital Content 2, http://links.lww.com/PRSGO/D722**). Over half of the participants (55%, n = 66 of 120) had 3 or more predictive risk-factors for amputation.

Baseline Wound Characteristics and Complexity

A total of 130 defects from 120 participants were included, with a median surface area of 7.5 cm^2 (IQR, 3.9—14.9 cm^2) (Table 3). There were 85 defects with age greater than 1 month (65.3%). A total of 107 (82.3%) wounds were DFUs, of which 46.7% (n = 50 of 107) were Wagner grade 3, and 24.3% (n = 26 of 107) were Wagner grade 4. Exposed structures (ie, bone, tendon or both) were present in 31 defects (23.8%) (Table 3). Osteomyelitis was confirmed in 47.7% of defects (n = 62 of 130). Defects were either CDC grade III (contaminated) (93.8%, n = 122) or CDC grade II (clean-contaminated) (n = 8, 6.2%).

Dermal Regeneration

OFM grafts were topically applied to regenerate dermal coverage in 125 defects (96.2%, n = 125 of 130) (Table 4). Seven patients were lost to follow-up (5.4%, n = 7 of 125) before complete granulation of the defect bed, and in 5 defects (3.8%, n = 5 of 125) the time to granulation tissue could not be determined, as the defect had epithelialized between follow-up visits. The time to granulation of the defect bed was estimated from KM survival analysis (Table 4; Fig. 2). The median time to complete granulation tissue coverage was 30.0 days (95% CI, 26.9–33.1) (Table 4, Fig. 2). Participants with exposed structures (n = 26; 20%) had a median time to granulation tissue coverage of 35 days (IQR, 27–57.8 days) (Table 4). One defect received a

Table 2. Patient Demographics

Characteristic	Value
Participants, n	120
Age (mean ± SD), median (IQR)	62.5 ± 14.1, 63.5 (53–71)
Sex	
Male, n (%)	85 (70.8)
Female, n (%)	35 (29.2)
Ethnicity	
Black or African American, n (%)	12 (10.0)
White, n (%)	95 (79.2)
Multiracial, n (%)	3 (2.5)
Other, n (%)	10 (8.3)
BMI, kg/m^2, median (IQR) [mean ± SD]	29.3 (26.4–35.7) [30.96 ± 7.49]
Tobacco use, n (%)	33 (27.5)
Diabetes mellitus	109 (90.8)
Controlled, n (%)	24 (20.0)
Uncontrolled, n (%)	85 (70.8)
Vascular disease	107 (89.2)
Venous, n (%)	4 (3.3)
Arterial, n (%)	43 (35.8)
Mixed, n (%)	27 (22.5)
Defects per patient, median (IQR) [mean ± SD]	1.0 (1.0–1.0) [1.1 ± 0.3]
ASA classification	
Class II, n (%)	8 (6.7)
Class III, n (%)	100 (83.3)
Class IV, n (%)	12 (10.0)

ASA, American Society of Anesthesiologists; BMI, body mass index .

Table 3. Baseline Defect Characteristics

Characteristic	Value
Defects, n	130
Defect size (cm^2), median (IQR) [mean ± SD]	7.5 (3.9–14.9) [11.3 ± 13.5]
Defect age	
<1 mo, n (%)	45 (34.6)
1–6 mo, n (%)	51 (39.2)
6–12 mo, n (%)	21 (16.2)
1–2 y, n (%)	12 (9.2)
5+ y, n (%)	1 (0.8)
Defect type	
DFU, n (%)	107 (82.3)
Wagner grade 2, n (%)	31 (29.0)
Wagner grade 3, n (%)	50 (46.7)
Wagner grade 4, n (%)	26 (24.3)
Surgical dehiscence, n (%)	8 (6.2)
Pressure injury—stage III, n (%)	4 (3.1)
Pressure injury—stage IV, n (%)	2 (1.5)
Superficial burn, n (%)	1 (0.8)
Traumatic, n (%)	5 (3.8)
Venous ulcer, n (%)	3 (2.3)
Exposed structures, n (%)	31 (23.8)
Bone, n (%)	24 (77.4)
Tendon, n (%)	1 (3.2)
Tendon and bone, n (%)	6 (19.4)
Osteomyelitis	
Yes, n (%)	44 (33.8)
No, n (%)	57 (43.8)
Suspected, n (%)	29 (22.3)
Confirmed positive postoperative, n (%)	18 (62.1)
Confirmed negative postoperative, n (%)	11 (37.9)
CDC grade, n (%)	
Grade II—clean-contaminated, n (%)	8 (6.2)
Grade III—contaminated, n (%)	122 (93.8)
Pain score—preoperative, median (IQR) [mean ± SD]	5 (3–6) [4.6 ± 1.5]

Table 4. Dermal Regeneration

Characteristic	Value
Defects, n (%)	125 (96.2)
LTFU (before complete granulation tissue), n (%)	7 (5.4)
Time to complete granulation tissue	
Defects, n (%)	113 (86.9)
Time, median (95% CI) [mean ± SEM], d	30.0 (26.9–33.1) [38.6 ± 2.8]
Incidence of complete granulation tissue	
30-d (95% CI)	48% (39%–57%)
60-d (95% CI)	85% (79%–92%)
90-d (95% CI)	94% (89%–98%)
Defects with exposed structures	
Defects, n (%)	26 (21)
Time to complete granulation tissue, median (IQR) [mean ± SD], d	35.0 (27.0–57.8) [48.4 ± 37.6]
Time to defect closure	
LTFU (before closure), n (%)	47 (36.1)
Defects closed, n (%)	78 (60.0)
Time, median (95% CI) [mean ± SEM], d	133.0 (113.2–152.8) [200.7 ± 16.6]
Incidence of defect closure	
90-d (95% CI)	31% (22%–40%)
120-d (95% CI)	45% (35%–55%)
180-d (95% CI)	60% (50%–70%)

LTFU, lost to follow-up; SEM, standard error of the mean.

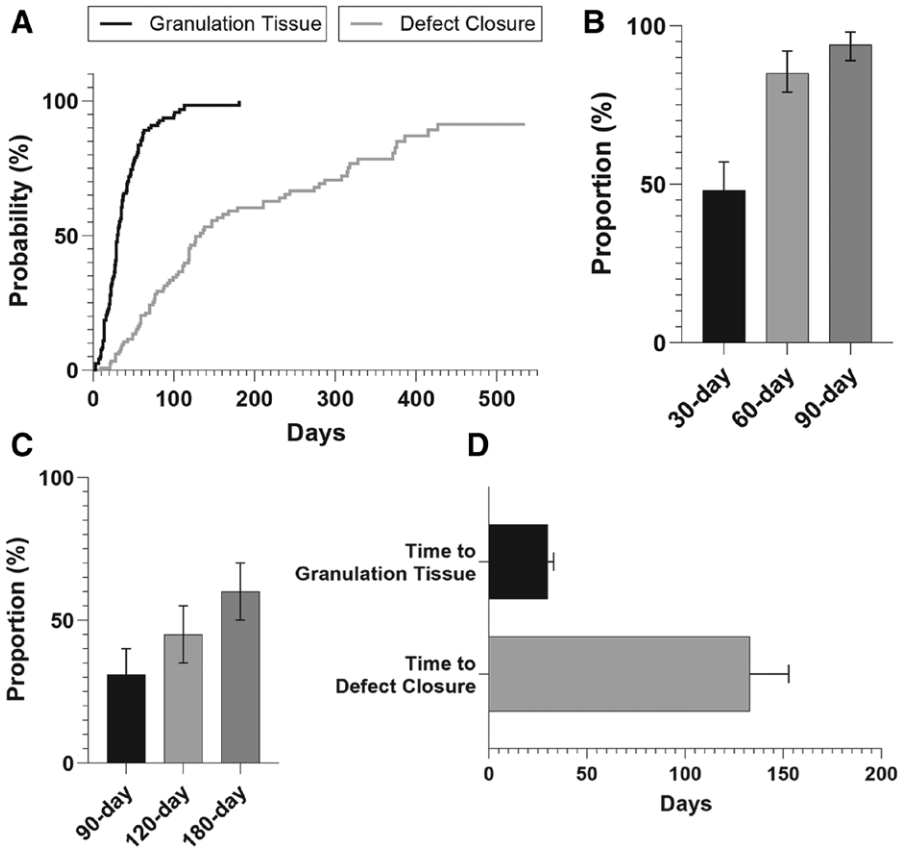

Fig. 2. Time to complete granulation tissue formation and time to closure of defects reconstructed via dermal regeneration. A, KM survival analysis of time to granulation tissue formation (solid black line) and time to defect closure (solid gray line). B, Incidence of complete granulation tissue coverage and/or fill at 30, 60, and 90 days; errors represent upper and lower 95% CI. C, Incidence of defect closure at 90, 120, and 180 days; errors represent upper and lower 95% CI of the median. D, Median time to granulation tissue formation and defect closure; errors represent upper and lower 95% CI.

split-thickness skin graft (STSG) at 13 days post-OFM graft application, and at 1-week, there was ~75% graft take. The remainder of defects were closed via secondary intention and managed with the same standard of care wound dressings (new contact layer, gauze, and elastic bandage for compression when indicated) and were changed weekly until 100% epithelialization was observed. The median time to closure was 133.0 days (95% CI, 113.2–152.8), as estimated from KM survival analysis (Table 4, Fig. 2).

Table 5. Closure by Primary Intention

Characteristic	Value
Defects, n (%)	5 (3.8)
LTFU (before closure), n (%)	0 (0.0)
Time to closure, median (IQR), [mean ± SD], (days)	26 (19–59) [36.2 ± 28.9]

LTFU, lost to follow-up.

Closure via Primary Intention

In 5 defects, OFM grafts were implanted subcutaneously, and defects closed via primary intention. The median time to closure, as judged by 100% epithelialization and the absence of drainage, was 26 days (IQR, 19–59 days) (Table 5).

Overall Closure Rates and Outcomes

The median follow-up period was 350 days (IQR, 107.3–441.8 days) (Table 6) across all 130 defects. At last follow-up there were no reported adverse events, surgical site infections, or postoperative complications reported. Of the 130 defects included in the study, 83 defects (63.8%) were followed up to final closure, with 47 (36.2%) being lost to follow-up before closure (Table 6, Fig. 1). Of the defects that closed, no recurrence of the index defect or major amputation was reported, at a median follow-up of 399 days (IQR, 343–470 days). The median time to complete closure for all defects (n = 130), estimated from KM survival analysis, was 127 days (95% CI, 110.5–143.5) (Fig. 3) (Table 6). A subgroup analysis of time to closure based on defect etiology is provided in Supplemental Digital Content 5. (**See table, Supplemental Digital Content 5**,

Table 6. Overall Closure Rates and Outcomes

Characteristic	Value
Maximum follow-up period, median, (IQR) [mean ± SD], d	350 (107.3–441.8), [288.9 ± 177.3]
Postoperative complications (deep tissue or superficial infection, seroma, hematoma, graft failure), n (%)	0 (0)
Time to defect closure	
LTFU, (before defect closure), n (%)	47 (36.2)
Achieved defect closure, n (%)	83 (63.8)
Time to close, median, (95% CI), [mean ± SEM], d	127.0 (110.5, 143.5), [193.7 ± 16.2]
Incidence of defect closure	
90-d (95% CI)	34% (25%–43%)
120-d (95% CI)	48% (38%–57%)
180-d (95% CI)	62% (52%–72%)
LOS, median (IQR) [mean ± SD], d	4 (1.25–8) [5.9 ± 7.8]
Patient reported pain score, median (IQR) [mean ± SD], n	1 (0–3) [1.6 ± 1.8], n = 18
Patient reported scar score, median (IQR) [mean ± SD], n	5.0 (5.0–5.0), [4.9 ± 0.2], n = 79
Total observer scar score, median (IQR) [mean ± SD], n	0 (0–0), [0.3 ± 0.6], n = 79

LOS, length of stay; LTFU, lost to follow-up; SEM, standard error of the mean.

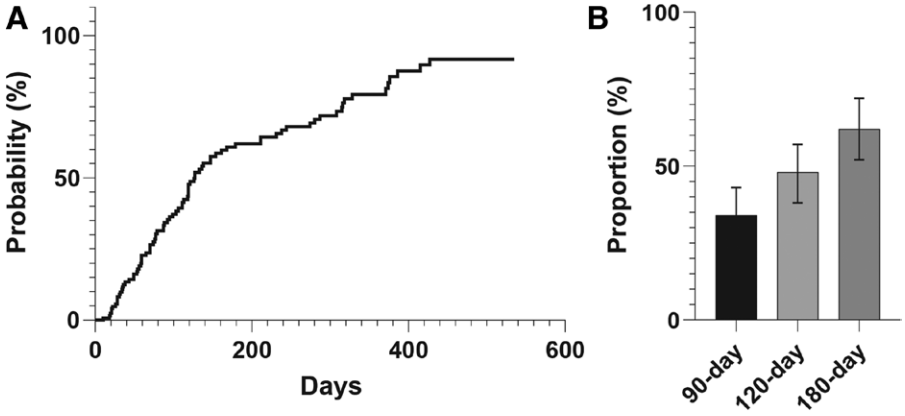

Fig. 3. Time to closure across all defects. A, KM survival analysis of time to closure for all defects. B, Incidence of defect closure at 90, 120, and 180 days; errors represent upper and lower 95% CI.

which displays the subgroup analysis, time to defect closure based on wound etiology, **http://links.lww.com/PRSGO/D725**.)

The median inpatient length of stay was 4 days (IQR, 1.25–8 days) (Table 6). The median patient reported pain score (n = 18) was 1 of 10 (IQR, 0–3), assessed at a median of 186 days (IQR, 47.3–373.3 days) after the initial surgery. Patient and surgeon reported scar assessments were highly satisfactory (**Supplemental Digital Content 2, http://links.lww.com/PRSGO/D722**).

Product Utilization and Cost

The median number of applications per defect was 1.0 (IQR, 1.0–1.0) (Table 7). A single OFM application was used in 79.2% of defects (n = 103 of 130), and a single defect received 6 applications. The majority of defects were treated with the OFM graft alone (63.1%, n = 82 of 130), or in combination with the OFM particulate (33.8%, n = 44 of 130) (Table 7). The median graft cost per defect across all 130 defects included in the study was US $253.90 (IQR, $253.90–$1238.00) (Table 7).

DISCUSSION

The current study focused on complex defects that required inpatient surgical reconstruction using OFM grafts as a component of the lower limb salvage algorithm. Patient reporting is drawn from a larger prospective registry study (NCT05243966) evaluating the use of OFM-based grafts across a wide range of soft-tissue defects. The study has been designed to evaluate patient outcomes with few inclusion and exclusion criteria. As such, the study design enables the prospective collection of outcomes data resembling real-world evidence studies. Many prospective studies and randomized controlled trials often exclude patients with confounding variables, such as patients with significant comorbidities (eg, uncontrolled diabetes), highly complicated or large wounds (eg, exposed structures and/or osteomyelitis).[4,26–31] Although these studies are important and well designed for specific outpatient populations, the outcomes have a narrow scope with respect to real-world challenges of managing these wounds.[32]

Enrolled participants presented with relatively complex lower extremity defects, including osteomyelitis,

Table 7. Product Applications and Cost

Product Applications	
Applications per defect, median (IQR) [mean ± SD]	1.0 (1.0–1.0) [1.4 ± 0.89]
1 Application, n (%)	103 (79.2)
2 Applications, n (%)	14 (10.8)
3 Applications, n (%)	8 (6.2)
4 Applications, n (%)	2 (1.5)
5 Applications, n (%)	2 (1.5)
6 Applications, n (%)	1 (0.8)
Product type	
OFM graft, n (%)	82 (63.1)
OFM particulate, n (%)	4 (3.1)
OFM graft and particulate, n (%)	44 (33.8)
Product costs	
Per defect cost, median (IQR) [mean ± SD] (US dollars)	$253.90 ($253.90–$1238.00), [$954.60 ± $1191.00]

Table 8. Product Cost Analysis

Product	OFM	BWMD	UBM	BTM	FBADM	FSG	eHAM
Cost to treat cohort—baseline (US dollars)	$84,465	$248,888	$131,268	$118,999	$144,153	$174,900	$72,290
% difference vs OFM	0	195	55	41	71%	107	–14
Product applications, median (IQR)	1.0 (1.0–1.0) (Table 7)	1.0 (1.0–1.0)[35]	1.0 (1.0–2.0)[40]	1.0 (1.0–1.0)[45]	1.0 (1.0–2.0)[39]	7.0 (3.0–16.0)[41]	1.0 (1.0–1.0)[34]
Median cost to treat cohort—w/product reapplication rates (US dollars) (IQR)	$84,465 ($84,465–$84,465)	$248,888 ($248,888–$248,888)	$131,268 ($131,268–$262,536)	$118,999 ($118,999–$118,999)	$201,814 ($172,983–$331,551)	$1,224,300 ($524,700–$2,798,400)	$72,290 ($72,290–$72,290)

which was present in ~48% of defects. Nearly 25% of participants had exposed structures (Tables 2, 3). Using a predictor model for LEA (**Supplemental Digital Content 1, http://links.lww.com/PRSGO/D721**), 95.8% of participants had at least one risk-factor for amputation. When taken collectively, this study reflects participants with complex wounds with comorbidities that represent a significant risk of lower limb amputation. Granulation tissue coverage and/or fill was achieved in a median of ~30 days across all wounds, and in ~35 days in those with exposed vital structures. More recently, OFM graft has been used as an implant under an advancing tissue flap to reduce surgical deep space and improve perfusion. The rationale for this approach is to reduce postoperative complications by reducing the risk of seroma, infection, and dehiscence of the primary closure.[22] Though only a small subset of participants were closed via primary intention (n = 5), with subcutaneous implant of the OFM graft, the median time to closure was ~26 days, and importantly, no postoperative complications were observed. Despite the participant and defect complexity, median time to complete closure across all defects was ~127 days (Table 6). All patients reported a high satisfaction score with 97.5% reporting a score of 5 of 5 (Table 6, **Supplemental Digital Content 2, http://links.lww.com/PRSGO/D722**).

These data align with a prior report evaluating the efficacy of reconstructing complex lower extremity soft tissue defects with OFM grafts.[24] In that study, the authors reported a median time to complete granulation tissue coverage of ~26 days and a mean time to closure of ~96 days.[24] Additionally, neither study reported postoperative complications or major amputations, underscoring the potential of OFM grafts to reduce these occurrences even in complex patients.

Literature Synthesis

A review of the literature was conducted to benchmark the results of the current study with previous reports of lower extremity reconstruction and limb salvage using dermal substitutes. (**See table, Supplemental Digital Content 6,** which displays literature synthesis, **http://links.lww.com/PRSGO/D726**.)

Identified studies described the following dermal substitutes: bilayer collagen-GAG wound matrix (BWMD), polyurethane biodegradable temporizing matrix (BTM), fetal bovine acellular dermal matrix (FBADM), urinary bladder matrix (UBM), esterified hyaluronic acid matrix (eHAM), and fish skin graft (FSG) (**Supplemental Digital Content 6, http://links.lww.com/PRSGO/D726**). Our current study had a relatively short time to granulation tissue formation (median, ~30 days) compared with the literature ranging from as low as 21[33] to ~23 days[34] to as high as 83 days.[35] Use of an STSG for definitive closure ranged from 15%[35] to 100% of cases,[36] which confounded comparing time to closure across the studies. Complete healing was reported as low as 74–84 days[33,37,38]; however, in 2 of the studies the majority of patients received an STSG in early stages of healing. In 3 studies, reported time to closure was notably longer at 182–198 days.[35,39,40] Incidence of infection ranged from 0%[24,41,42] to ~42%–48%.[40,43] Of the studies describing the use of synthetic dermal substitutes (BTM and BWMD) infection rates ranged from 3.3%[33] to 20%.[44–47] Another

outcome applicable only to the synthetic dermal matrices (BTM, eHAM, and BWMD) is the incidences of graft loss, which ranged from 2.8%[36] to 19%.[35] The decellularized ECM-based grafts such as OFM, UBM, FSG, and FBADM could require repeat product applications. For example, Lullove et al[38] reported a median FBADM reapplication of 1.4 (IQR, 1.2–2.3), whereas Mundra et al[40] reported a median reapplication rate of 1.9 (IQR, 1.0–2.0) for UBM. Published studies for FSG report median reapplication rates of up to 7.0 (IQR, 3.0–16.0).[41] In our current study, the median product application was 1.0 (IQR, 1.0–1.0). Studies reported amputation rates from ~5%[40,41,46] up to 23.5% following reconstruction with BWMD.[43]

Product Cost Analysis

The cost of dermal matrices identified in the literature review varies widely (**Supplemental Digital Content 6**, **http://links.lww.com/PRSGO/D726**), and it is important to consider the cost of any new product versus the clinical outcomes. The cost analysis was undertaken by considering all the dermal substitutes with published evidence in the reconstruction of complex lower extremity defects (**Supplemental Digital Content 6**, **http://links.lww.com/PRSGO/D726**). The cost of treating the current cohort (n = 130) using OFM grafts versus alternates was calculated based on publicly available device costs and the known sizes of graft applied to each defect. (**See table, Supplemental Digital Content 7**, which displays publicly available product costs, **http://links.lww.com/PRSGO/D727**.) This analysis first assumed that a single application of each of the dermal substitutes was required to treat each defect from the current study to provide a baseline cost to treat the cohort (Table 8). The device costs to treat the current cohort with OFM were $84,465, and for the other dermal substitutes ranged from $72,290 (eHAM) to $248,888 (BWMD). With the exception of eHAM, all other dermal substitutes resulted in a substantial cost increase compared with OFM grafts, in some cases up to 3 times higher. Second, the analysis took into account the product reapplication rate of the dermal substitutes based on published data (**Supplemental Digital Content 6**, **http://links.lww.com/PRSGO/D726**). UBM, FBADM, and FSG have reported product reapplication rates ranging up to 7 devices per defect. This additional expense has significant impact on the overall cost to treat lower extremity defects. For example, taking into account a median reported application rate of FSG of 7.0 (3.0–16.0),[41] the cost of this product compounds to an estimated median cost to treat the cohort of $1,224,300 ($524,700–$2,798,400), which is 14 times higher than OFM. The cost analysis (Table 8) did not take into account the cost of postoperative complications (eg, infections, amputations) or the costs associated with weekly postoperative dressing changes.

CONCLUSIONS

The current study demonstrates the safety of OFM-based grafts when used to augment the surgical reconstruction of complex lower extremity soft-tissue defects. Granulation tissue coverage and fill was achieved in a cohort with known risk factors for limb amputation, significant medical comorbidities, and defects that included osteomyelitis, contamination or infection, and exposed structures. There were no adverse events, graft failure, surgical site infections, or other postoperative complications, suggesting OFM grafts may provide a cost-effective alternate to other dermal substitutes in this surgical application. Limitations of this study include the lack of a comparative arm and the inability to control for patient demographics, health history, and comorbidities due to the real-world nature of the study design.

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DISCLOSURES

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