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Combining antibiotic-loaded bone cement-based free vastus lateralis muscle-sparing flap with split-thickness skin grafts: A reliable strategy for reconstructing diabetic foot ulcers at non-weight-bearing areas

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Abstract

Diabetic foot ulcers (DFUs) present significant challenges due to their associated amputation rates, mortality, treatment complexity and excessive costs. Our earlier work introduced a wound surgical integrated treatment (WSIT) for DFUs, yielding promising outcomes. This study focuses on a specific WSIT protocol employing antibiotic-loaded bone cement (ALBC) in the first Stage, and free vastus lateralis muscle-sparing (VLMS) flaps and split-thickness skin grafts (STSGs) in the second stage to repair non-weight-bearing DFUs. From July 2021 to July 2023, seven DFU patients (aged 47–71 years) underwent this treatment. Demographic data, hospital stay and repair surgery times were collected. Histological and immunohistochemical analyses assessed angiogenesis, collagen deposition and inflammation. SF-36 questionnaire measured pre- and postoperative quality of life. Preoperative ultrasound Doppler showed that the peak blood flow velocity of the recipient area artery was significantly >30 cm/s (38.6 ± 6.8 cm/s) in all patients. Muscle flap sizes varied from 8 × 3.5 × 1 to 18 × 6 × 2 cm. The operation time of the repair surgery was 156.9 ± 15.08 minutes, and the hospital stay was 18.9 ± 3.3 days. Histological analysis proved that covering DFUs with ALBC induced membrane formation and increased collagen, neovascularization and M2 macrophages fraction while reducing M1 macrophages one. All grafts survived without amputation during

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a 7- to 24-month follow-up, during which SF-36 scores significantly improved. A combination of ALBC with free VLMS flaps and STSGs proved to be safe and effective for reconstructing non-weight-bearing DFUs. It rapidly controlled infection, enhanced life quality and foot function, and reduced hospitalization time. We advocate integrating this strategy into DFU treatment plans.

KEYWORDS

bone cement, diabetic foot ulcer, limb salvage, reconstructive surgery, vastus lateralis

Key Messages

- This study proposed a reliable strategy for reconstructing DFUs at non-weight-bearing areas.
- Histology and immunofluorescence studies confirmed that covering DFUs with ALBC after debridement induced the formation of a membrane, helped control foot infection, promoted wound collagen deposition and vascular regeneration and mitigated inflammation, altogether advancing wound healing.
- This protocol provides a good appearance, rebuilds foot function and improves the quality of life of these DFU patients.

1 | INTRODUCTION

Diabetic foot ulcers (DFUs) result from varying degrees of diabetic peripheral neuropathy (DPN), infection and peripheral artery disease (PAD).[1] The global DFU incidence is approximately 6.3%.[2] Hence, DFUs must be considered as essential targets of diabetes prevention and treatment. DFUs are one of the leading causes of lower limb amputations in diabetic patients.[3] Worldwide, roughly one patient every 30 s undergoes an amputation due to DFUs.[4] Additionally, after a major limb amputation, from 39% to 80% of DFU patients will die within 5 years.[5] Furthermore, DFUs treatments entail high costs,[3] negatively affect patient's quality of life (QOL)[6] and cause severe social and psychological problems to them.[7]

In recent years, the multidisciplinary team (MDT) approach has been regarded as the ideal solution for DFU management.[1,8,9] Musuuza et al.[9] identified four critical tasks for MDTs managing DFUs: blood glucose control, local wound care, PAD's diagnosis and therapy and infections' control. As regards managing local wounds, PAD and DPN, we have proposed a wound surgical integrated treatment (WSIT) mode.[10] The core of WSIT includes debridement, revascularization, ALBC filling and free tissue/skin grafting to reduce amputation and mortality rates, thereby improving QOL. Our early research in this field achieved exciting results.[11–14]

Free muscle flaps are a procedure of free tissue transfer for reconstructing DFUs, which we included in WSIT in this study.[15,16] Jiga et al.[17] combined the VLMS flap with split-thickness skin grafts (STSGs) to reconstruct 18 cases of plantar foot defects, including six patients with DFUs. All VLMS flaps survived, and there was a significant improvement in foot function. The authors believed that the VLMS flap was a better option than other muscle flaps (such as the gracilis, rectus abdominis, serratus anterior and gastrocnemius muscles). However, more detailed reports on VLMS applications are still needed, specifically regarding DFUs.

In our WSIT model, a series of diabetic foot reconstruction plans were implemented.[11–14] As to the present case series, we introduced the experience of Stage I, which involves after DFU debridement using an ALBC filling, and of Stage II, which entails utilizing a VLMS flap combined with a STSGs to reconstruct the non-weight-bearing area DFU. Our goal is to provide a comprehensive solution for the reconstruction and management of DFU patients.

2 | PATIENTS AND METHODS

2.1 | Identification and evaluation of candidates for DFU reconstruction

We previously reported a multidisciplinary assessment method for DFU patients.[10] Upon admission, all patients were immediately enrolled in the MDT for perioperative management and Stage I treatment of the local wound.

The main components included medical history inquiry, physical examination, laboratory tests and imaging examinations to fully evaluate the patients' overall condition, local wound aspect and lower limb circulation, as shown in Figure 1.

The medical history, physical examination and imaging assessments were conducted according to the multidisciplinary approach of Wang et al.[1] In particular, in our Institution, it is considered as proper that patients' fasting blood glucose (FBG)values fall between 3.9 and 7.2 mmol/L, postprandial blood glucose (PBG) values range from 6.1 to 11 mmol/L and GHbA1C be <8.0%.[11–14] CT angiography and foot MRI or X-ray were performed to assess the patency of blood vessels and infection status, as well as to determine the debridement's scope and ALBC's use.

In Stage II, a comprehensive assessment of the patient's overall health and the local wound's specific condition must guide the drawing up of a treatment plan for wound management. We compiled a set of indications

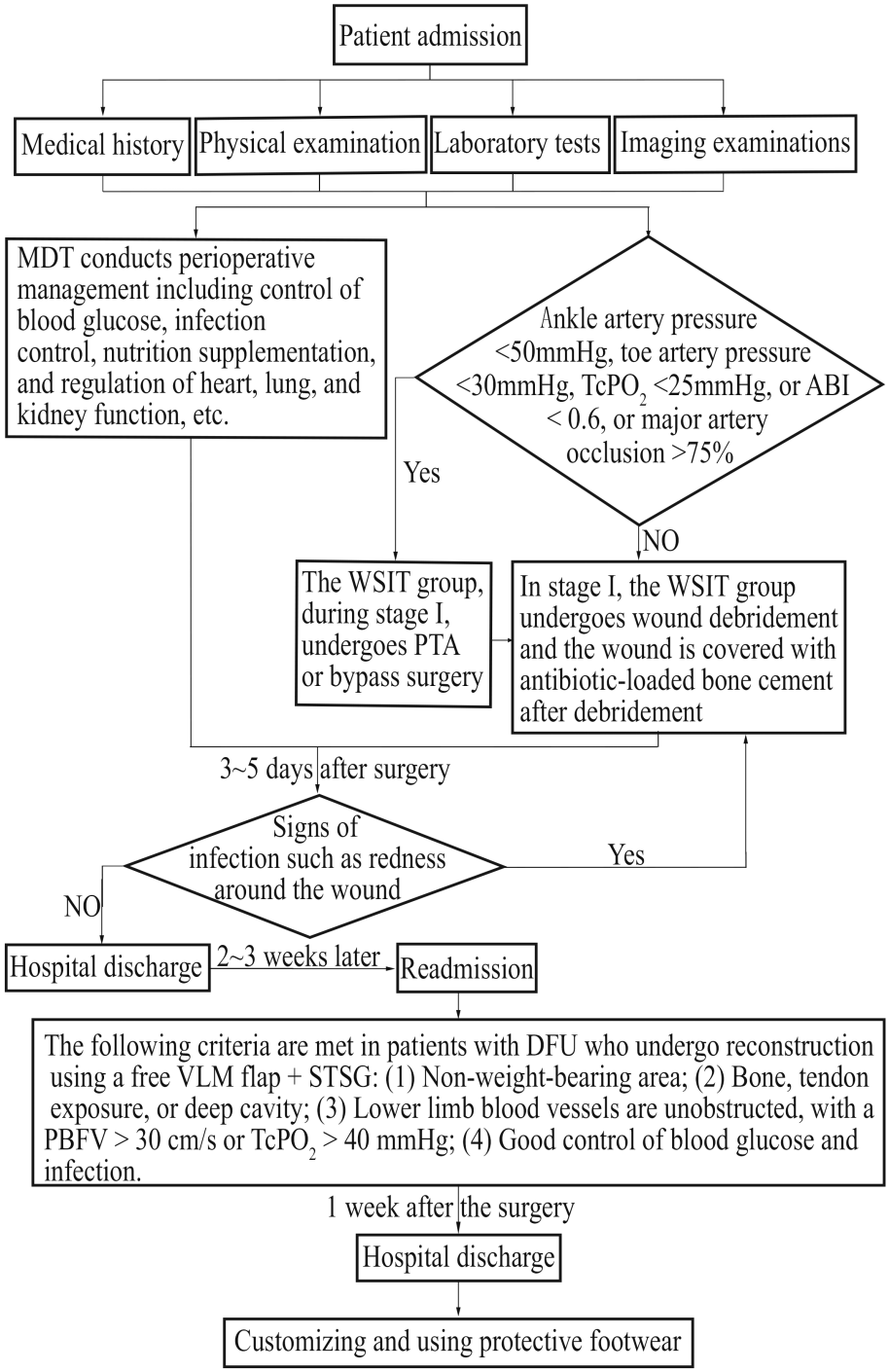

FIGURE 1 The detailed algorithm used for reconstructing non-weight-bearing area DFUs by the ALBC-based combination of free VLMS flap and STSG transplantation. ABI, Ankle Brachial Index; DFU, Diabetic Foot Ulcer; MDT, Multiple Disciplinary Team; PBFV, Peak Blood Flow Velocity; PTA, Percutaneous Transluminal Angioplasty; STSG, Split-thickness Skin Graft; $TcPO_2$, Transcutaneous Oxygen; VLMS, Vastus Lateralis Muscle Sparing; WSIT, Wound Surgical Integrated Treatment.

and contraindications about the use of free tissue flap transfers to reconstruct DFUs.[18] Briefly, the VLMS flap application and STSGs for DFU reconstruction are recommended under the following conditions: (*i*) Type 1 or Type 2 DFU patients presenting with an exposed bone or tendon or with a necrotic cavity in non-weight-bearing areas. (*ii*) Adequate blood flow in the lower limbs,[19] characterized by a minimum of two patent arteries supplying their distal portions and a peak blood flow velocity (PBFV) exceeding 30 cm/s.[20] (*iii*) Controlled infection of the DFU post-initial debridement and ALBC covering, with the absence of any purulent discharge. (*iv*) Recent blood glucose tests with stable values. (*v*) No latter-day acute complications such as diabetic coma or ketoacidosis. Conversely, the contraindications encompass: (i) Patients with end-stage diabetic nephropathy and uraemia needing long-term dialysis. (*ii*) Proximal or multiple occlusion and severe stenosis of major arteries. (*iii*) Uncontrolled infection.

2.2 | Preparation of the wound bed at the recipient site

Based on the extent and depth of tissue necrosis and infection and the involved area of the foot, we performed thorough debridement procedures to remove infected and necrotic skin, muscle, tendon and bone tissues. Thereafter, the wound surface was covered, and its cavity was filled with ALBC, that is PALACOS R + G-High-Viscosity Bone Cement with Gentamicin® (Heraeus, Germany). Vancomycin (2 g per 40 g mix) was added to the ALBC powder before mixing it with the fluid. Drainage holes were drilled in the bone cement, which was then secured to the wound using 4# silk sutures. The surgeons should wait until the bone cement mixture temperature has significantly decreased before covering the wound to avoid any heat-caused damage to the soft tissue. Next, sterile dressings were applied and changed every 2–3 days. The bone cement was removed 2-to-3 weeks later. If the wound infection were under control and a transparent gel-like 'induced membrane' had formed, a free VLMS flap repair of the wound could be performed after a second debridement.

2.3 | Free VLMS flap combined with STSGs

A 10–20 cm longitudinal incision was made on the medial side of the ilio-patellar line, and the skin and fascia lata were cut to expose the VLMS. Next, the VLMS was separated from the rectus femoris muscle, and the descending branch of the lateral circumflex femoral artery (LCFA), along with its accompanying nerve, was found and dissected downward. Afterwards, the VLMS flap was designed and harvested according to the wound's needs; the nerve was kept in its original position. VLMS superficial and intermediate partitions were typically enough for repair purposes. At the same time, it was imperative to keep the deep aponeurosis to uphold the continuity between the muscle's origin and insertion. Then, the VLMS flap was transplanted onto the recipient site. An end-to-end or end-to-side anastomosis of the descending branch of LCFA was set up with the anterior/posterior tibial artery. An end-to-end anastomosis of the accompanying veins of the VLMS flap was put in place with the anterior/posterior tibial veins or subcutaneous veins at the recipient site. Finally, an STSG from the thigh or scalp was taken to cover the VLMS flap.

2.4 | Postoperative protocol

Postoperatively, the patient's FBG and PBG levels must be continuously checked to ensure they stay within the above-mentioned ranges. Patients were to be instructed to see bed rest and strictly avoid smoking. Adequate fluid supplements were ensured to upkeep the flap's perfusion. Routine measures needed to be implemented to keep the patient warm and support analgesia, while anticoagulant medications were administered when needed. Close observation of the flap's colour, degree of swelling, temperature levels and any bleeding occurring within the first week after surgery was crucial to evaluate the flap's blood supply. The patient could be discharged once the flap was stable, usually within 7 to 10 days after surgery. After discharge, the patient was recommended to check blood glucose levels and blood pressure values. A clinical physician conducted a follow-up through a smartphone, checking the patients' condition. A follow-up visit was recommended after 2 weeks to remove sutures. Between 4 and 6 weeks post-surgery, the use of customized therapeutic shoes was suggested based on the place of the flap to reduce the risk of ulcer recurrence.

All patients completed the SF-36 questionnaire upon admission. During the final follow-up, an assessment for reported health improvement was not conducted since the follow-up time of some patients did not exceed 1 year.

2.5 | Histology and immunofluorescence (IF)

After debridement and filling with ALBC, each patient's samples of wound bed tissues were embedded in paraffin. The specimens were then cut into 3-μm-thick sections

using an ultrathin microtome. Haematoxylin–eosin (HE) staining was performed using reagents from Solarbio (China). Masson's Trichrome staining reagents were from MXB® Biotechnologies (China). In both cases, the sellers' instructions were followed. The stained tissue sections were seen under the microscope at low and high magnifications. NIH Image J software served to assess the specimens' collagen deposition and calculate the collagen volume fraction (CVF).

For IF, tissue sections were sequentially fixed with 4% paraformaldehyde for 30 min, dipped into 0.1% Triton X-100 for 10 min, and incubated with 5% bovine serum albumin for 30 min. Next, the samples were exposed overnight at 4°C to one of the following primary antibodies against: CD31 (1:1000, #ab182981, Abcam, USA); CD 206 (1:5000, #18704-1-AP, Proteintech, USA); iNOS (1:800, #A3774, ABclonal, USA). Subsequently, the sections were rinsed and incubated at room temperature for 2 h with the corresponding secondary antibodies. Finally, samples were photographed using a fluorescence microscope after staining the nuclei with 4′,6-diamidino-2-phenylindole (DAPI) for 5 min. $CD31^+$ blood vessel counts were performed in 4–5 randomly selected high-powered fields per patient.

2.6 | Statistical analyses

All SF-36 questionnaire data and non-normally distributed data were expressed using medians and ranks, and the Mann–Whitney *U*-test was employed to analyse any differences before and after surgery. For the rest of the data, the normally distributed variables were expressed as means ± standard deviation (SD), and Student's *t*-test was used to compare them. All analyses were conducted using the SPSS 29.0 software package (IBM Corp., Armonk, NY, USA, Version 29.0). p values <0.05 were taken as statistically significant.

3 | RESULTS

3.1 | Patients' information

This case series included seven patients with type 2 diabetes, aged 47 to 59. Five were males, and two were females, with DFU durations between 5 and 11 months. All patients had various local infection symptoms, including redness, swelling, ulcers and necrosis. Among them, there was one case of Wagner grade 2 DFUs, two cases of Wagner grade 3 DFUs and four cases of Wagner grade 4 DFUs. CTA scans revealed no central arterial occlusion (i.e., >75%) in their lower extremities. Preoperative lower limb vascular colour Doppler ultrasound tests showed PBFV >30 cm/s (38.6 ± 6.8 cm/s) in all recipient areas.

The operative time of the repair surgery lasted 156.9 ± 15.08 min. In six patients, the anterior tibial artery served as the anastomotic artery, while in the remaining one, the posterior tibial artery was used. The accompanying veins from the recipient sites functioned as anastomotic veins. All muscle flaps were anastomosed to one artery and two veins. All muscle flaps and STSGs survived postoperatively with no significant complication and had a soft texture. The average length of hospital stay (LOS) was 18.9 ± 3.3 days. Follow-ups were conducted for 7 to 24 months (Table 1). All patients achieved limb salvage, with no complications occurring during the follow-up period. Patients were able to independently get out of bed and walk, experiencing a significant improvement in their QOL compared to preoperative conditions ($p < 0.05$) (Table 2).

3.2 | Histology and IF

HE staining and macroscopic observations showed that 2 to 3 weeks after the wound had been covered with ALBC, an 'induced membrane' had formed (Figure 2A,B). Masson's staining showed a significant increase in collagen deposition. CVF was significantly higher after filling with ALBC as compared to before surgery (20.41 ± 5.78% vs. 41.10 ± 5.20%, $p < 0.0001$) (Figure 2C,D). IF revealed a significantly increased neovascularization ($CD31^+$ blood vessels: preoperatively: 6.57 ± 2.44/HPF, postoperatively: 9.71 ± 2.56/HPF, $Pp < 0.05$) (Figure 3). After filling with ALBC, IF also showed at DFU sites a decrease in M1 macrophages ($iNOS^+$ cells: preoperatively: 24.29 ± 1.89/HPF, postoperatively: 7.14 ± 1.95/HPF, $p < 0.0001$) (Figure 4A,B) and an increase in M2 macrophages ($CD206^+$ cells: preoperatively: 9.43 ± 3.51/HPF, postoperatively: 182.14 ± 44.54/HPF, $p < 0.0001$) (Figure 4C,D).

3.3 | Typical cases report

3.3.1 | Case 1

A 54-year-old male with diabetes and dorsal DFU (size: 6 × 3 × 0.7 cm) on the left foot. Successful reconstruction was achieved through the WSIT model (Figure 1). In simple terms, after admission, the MDT conducted perioperative management to reduce surgical risks. Following debridement by the WSIT team in stage I, the wound was covered with ALBC (Figure 5A). In stage II, after

TABLE 1 Patients' information.

Case	Sex/age (years)	Duration of DFUs (months)	Comorbidity	Operation time (minutes)	DFU size (cm × cm × cm)	Wagner grade	DFU Location
1	M/54	6	NO	135	6 × 3 × 0.7	2nd grade	Dorsal
2	M/52	10	PAD, CRF	160	12 × 4 × 0.8	3rd grade	Lateral
3	M/56	8	DPN	150	10 × 3.5 × 1.2	4th grade	Intermetatarsal
4	M/44	5	NO	165	11 × 3.5 × 2	4th grade	Intermetatarsal
5	F/53	11	CRF	186	16 × 5 × 2	4th grade	Dorsal
6	F/59	7	PAD, DPN	145	10 × 5 × 1.4	4th grade	Lateral, dorsal
7	M/47	9	NO	157	8 × 4 × 0.8	3rd grade	Medial, dorsal

VLMS flap (cm × cm × cm)	Pedicle length (cm)	Recipient artery/ anastomosis	PBFV in recipient artery (cm/s)	LOS (days)	Follow-up (months)	Outcome
8 × 3.5 × 1	6	PTA/EEA	40	17	12	Walking
14 × 4 × 1	10	PTA/EEA	35	15	7	Walking
12 × 5 × 1	11	PTA/EEA	38	18	8	Walking
12 × 5 × 2	12	PTA/EEA	40	20	24	Walking
18 × 6 × 2	4	PTA/EEA	34	24	9	Walking
12 × 6 × 1.5	9	ATA/ESA	31	22	7	Walking
9 × 5 × 1	12	PTA/ESA	52	16	11	Walking

Abbreviations: ATA, anterior tibial artery; CRF, chronic renal failure; DFUs, diabetic foot ulcers; DPN, diabetic peripheral neuropathy; EEA, end-to-end anastomosis; ESA, end-to-side anastomosis; LOS, length of (hospital) stay; PAD, peripheral artery disease; PBFV, peak blood flow velocity; PTA, posterior tibial artery; VLMS, vastus lateralis muscle sparing.

removing the ALBC, the induced membrane formation and tendon exposure could be seen (Figure 5B). Therefore, we opted for a free VLM flap (size: 8 × 3.5 × 1 cm) and a thigh STSG for reconstruction (Figure 5C,D). At the 12-month follow-up, the patient could ambulate normally, the flap showed a full and soft appearance (Figure 5E), knee joint function was normal and the donor site only presented a minor scar that could be well concealed (Figure 5F).

3.3.2 | Case 4

A 44-year-old male with diabetes and an intermetatarsal DFU (size: 11 × 3.5 × 2 cm) on the left foot. Successful reconstruction was achieved through the WSIT model (Figure 1). In simple terms, after admission, the MDT conducted perioperative management to reduce surgical risks. Following debridement by the WSIT team in Stage I, the wound was covered with ALBC (Figure 6A–D). In Stage II, after removing the ALBC, the formation of an 'induced membrane' and a cavity could be seen (Figure 6E,F). Therefore, we chose a free VLMS flap (12 × 5 × 2 cm) and a scalp STSG for reconstruction (Figure 6G–J). At the 24-month follow-up, the patient could ambulate normally, and the flap had a full and soft appearance (Figure 6K,L).

4 | DISCUSSION

In the present work, we described the surgical outcomes of seven patients with a non-weight-bearing zone DFUs that were treated for reconstruction with ALBC-based free VLMS flaps combined with STSGs. In our case series, we found that covering the wound with ALBC after the Stage I debridement could advance the formation of an 'induced membrane', quickly control infection, promote granulation tissue growth and vascular regeneration, improve wound perfusion (Figures 2–4) and ease the survival of the free tissue. Additionally, it could also shorten hospital stays (Table 1). For Stage II non-weight-bearing zone DFUs, reconstruction with a VLMS flap combined with an STSG could improve lower limb function, enable independent walking and improve patients' QOL (Table 2).

DFU patients often present complications such as DPN, PAD, chronic renal failure (CRF), end-stage renal disease (ESRD) and infection, as shown in our case series. These factors make DFU repair extremely challenging and typically require an MDT management. Our proposed WSIT,[10] which combines wound debridement, vascular reconstruction, ALBC filling and free muscle tissue/skin grafting, had shown an initial effectiveness.[11–14] MDT perioperative management effectively addresses critical issues, including local wound management,

TABLE 2 Quality of life assessments of seven DFU patients treated with the ALBC-based combination of free VLMS flap and STSG.

Case no.	PF		RP		BP		GH		VT		SF		RE		MH	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	25	90	0	100	100	22	15	77	25	80	25	100	33.3	100	20	80
2	15	95	0	100	84	32	5	82	20	85	37.5	100	0	100	36	84
3	20	95	25	75	51	12	20	75	30	70	12.5	87.5	0	33.3	52	84
4	10	100	0	75	84	24.5	20	85	40	90	12.5	100	33.3	100	56	92
5	0	95	0	50	100	21	10	65	40	85	12.5	75	0	100	48	80
6	30	80	0	75	51	12	10	55	25	85	25	75	33.3	66.7	36	84
7	40	100	0	100	100	41	30	95	50	95	50	100	33.3	100	68	84
Median (range)	20 (0–40)	95 (80–100)	0 (0–25)	75 (50–100)	84 (51–100)	22 (12–24)	15 (5–30)	77 (55–95)	30 (20–50)	30 (70–95)	25 (12–50)	100 (75–100)	33.3 (0–33.3)	100 (33.3–100)	48 (20–68)	84 (80–92)
P-value	0.002*		0.001*		0.002*		0.002*		0.002*		0.001*		0.002*		0.002*	

Note: The *p*-value was obtained by comparing data at admission with the last follow-up after surgery.
Abbreviations: BP, bodily pain; DFUs, diabetic foot ulcers; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP: role physical; SF, social functioning; STSG, split-thickness skin graft; VLMS, vastus lateralis muscle sparing; VT, vitality.
*Statistically significant, $p < 0.05$.

diagnosis and treatment of PAD, and diagnosis and control of infection.

Most DFU infections are polymicrobial, with *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* being the primary pathogens.[21,22] In recent years, ALBC has been used to treat DFUs[23–26] as it is mixed with antibiotics such as gentamicin, tobramycin and vancomycin.[27] This mixture can continuously release antibiotics locally, slowly and effectively killing the bacteria commonly infecting DFUs, thus avoiding the systemic side effects of medications.[28] Additionally, ALBC has been proven to rapidly control infection, promote ulcer healing, shorten hospital stays and lessen medical costs.[23–26] In our case series, the overall average hospital stay for patients was 18 days, which is lower than the 31 days (range: 12–51 days) reported in the systematic review by Bhat et al.[29] Besides releasing antibiotics, the ALBC treatment for DFUs promotes the formation of the 'induced membrane' (Figure 2B).[23,26] It can also cause the production of various cytokines, such as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β).[30] These factors stimulate granulation tissue growth (Figure 2A), increase collagen deposition (Figure 2C), advance revascularization (Figure 3) and regulate the local inflammatory responses through the transition of macrophages from the M1 to the M2 phenotype (Figure 4). As a result, they improve local wound perfusion, nurture a favourable wound bed, ease later tissue repair and increase the graft survival rate.

The use of free tissue transfer for DFU reconstruction has been controversial due to factors such as poor blood glucose control, DPN, PAD, ESRD and infection. Recent studies showed that the success rate of free tissue reconstruction for DFUs is about 92%,[15,31] with a complete loss rate of 7.14%.[32] Free flaps can reduce amputation and mortality rates,[15,31,33–35] with limb salvage rates ranging from 83.4% to 93.7%.[15,31,34] Oh et al.[34] reported a limb salvage rate of 84.9% and a 5-year survival rate of 86.8% after an average follow-up of 53.2 months. In addition, consistent with earlier reports,[34] our case series showed overall QOL improvements (Table 2). Combining free VLMS flaps with STSGs reconstruction can provide proper wound contouring (Figures 5 and 6) and enable walking ability (Table 1).[11,13,14] However, although Chen et al.[36] reported no significant difference in complications between free flaps and pedicled flaps used for lower limbs of diabetic patients, we hold that a comprehensive preoperative evaluation and the correction of adverse factors are essential in MDT.

Muscle flaps used for DFU reconstruction were reported between the 1970s and the 1980s.[37] A systematic review indicated that the most commonly used local intrinsic muscle flap is the abductor digit minimi, followed by abductor hallucis, flexor digitorum brevis,

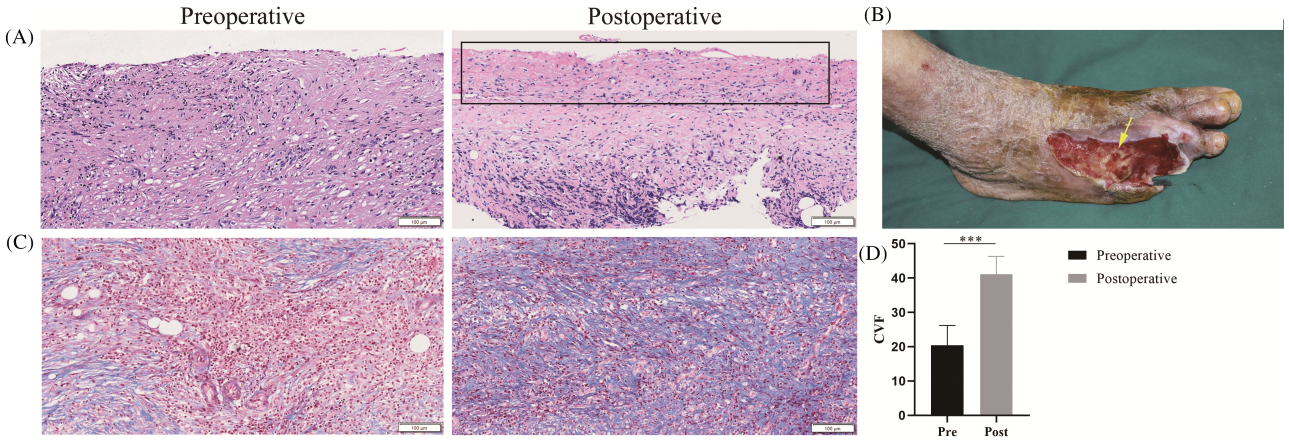

FIGURE 2 Covering the wound with ALBC promoted the formation of the 'induction membrane' and increased local collagen deposition. (A) HE staining of DFUs' wound bed tissue before covering it with ALBC, and after this procedure, the formation of the 'induction membrane' (box selection). (B) The macroscopic image of a typical 'induction membrane'. *Yellow arrow*, the gel-like 'induction membrane'. (C) After the wound was covered with ALBC, Masson staining revealed a noticeable increase in collagen deposition in the wound bed as compared to the preoperative condition. (D) Pre- and postoperative semi-quantitative measurements revealed a significant elevation of the collagen amounts compared to the condition before the covering with antibiotic-load bone cement ($n = 7$, $^{***}p < 0.0001$). Scale bar: 100 μm. CVF, Collagen Volume Fraction; HE, Haematoxylin Eosin.

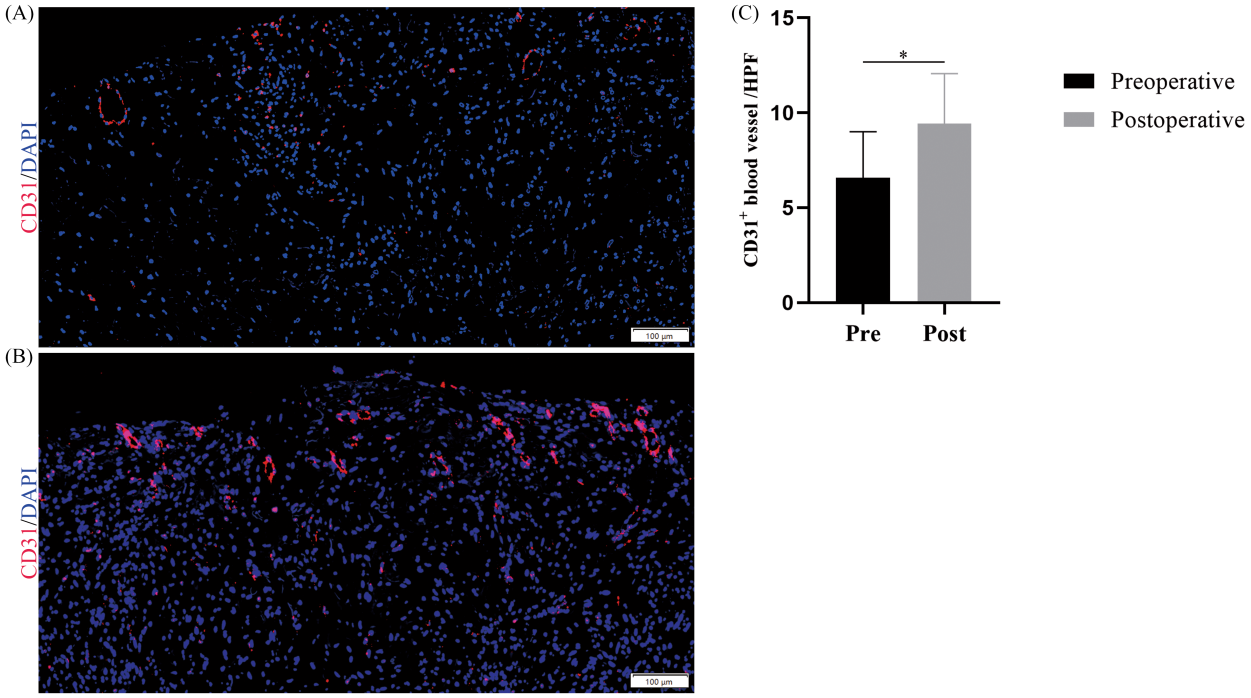

FIGURE 3 Covering the wound with ALBC enhanced small vessel neoformation. (A, B) The induction membrane sections were immunostained to reveal CD31 (red). Blue nuclei were stained with DAPI. Small vessels could be seen inside the newly formed 'induction membrane'. (C) Semi-quantitative measurements of immunostained sections revealed a postoperative significantly higher number of blood vessels as compared to preoperative conditions ($n = 7$, $^{*}p < 0.05$). Scale bar: 100 μm. CD31, Cluster of Differentiation 31 (also named Platelet Endothelial and Cell Adhesion Molecule-1); DAPI, 4′, 6-diamidino-2-phenylindole; HPF, high power field.

extensor digitorum brevis and flexor digit minimi. The reported overall success rate of these flaps was 87%,[38] which is significantly lower than the success rate of free tissue reconstruction (approximately 92%).[15,31] However, local muscle flaps can only provide a small amount of tissue, making them suitable for reconstructing small ulcers but not moderate to large size ulcers. Moreover, Kim et al.[39] believed that atherosclerotic changes and calcifications in the foot arteries of DFU patients are more severe than in the blood vessels of other sites. Therefore,

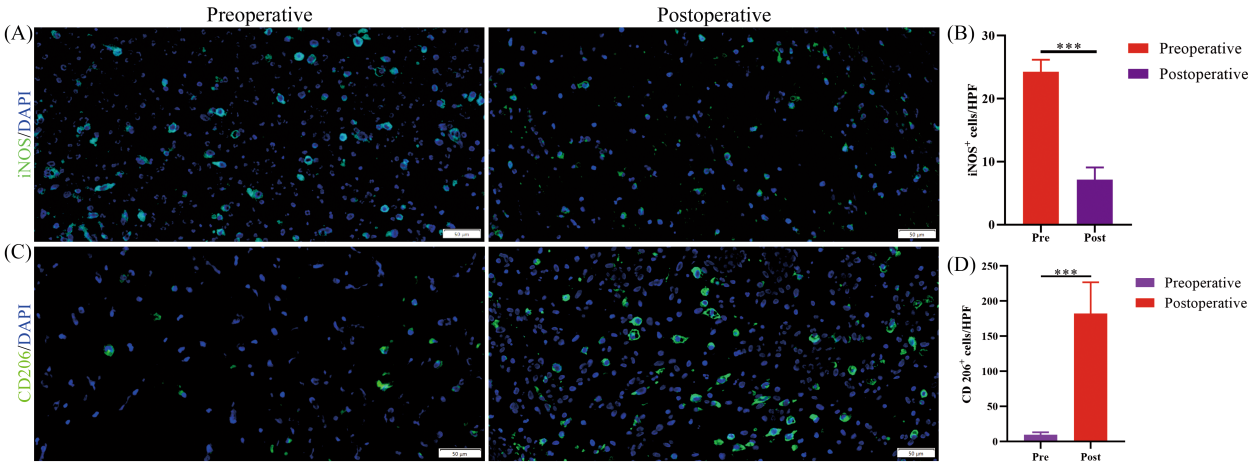

FIGURE 4 Covering the wound with ALBC can regulate the local inflammatory responses through M1 and M2 macrophages. (A, C) Representative images of immunofluorescence staining of inducible nitric oxide synthase (iNOS) antibody (green) for M1 macrophages and CD260 (green) for M2 macrophages from the wound bed of stage I after debridement and the wound bed (holding induced membrane) after removal bone cement before wound repair. Postoperatively, a significant decrease in M1 macrophages and an increase in M2 macrophages were seen compared to the preoperative conditions. (B, D) Semi-quantitative measurements showed that M1 macrophages population was significantly reduced, while that of M2 macrophages were significantly increased. ($n = 7$, $^{***}p < 0.0001$). Scale bar: 50 μm. DAPI, 4′,6-Diamidino-2-Phenylindole; HPF, high power field.

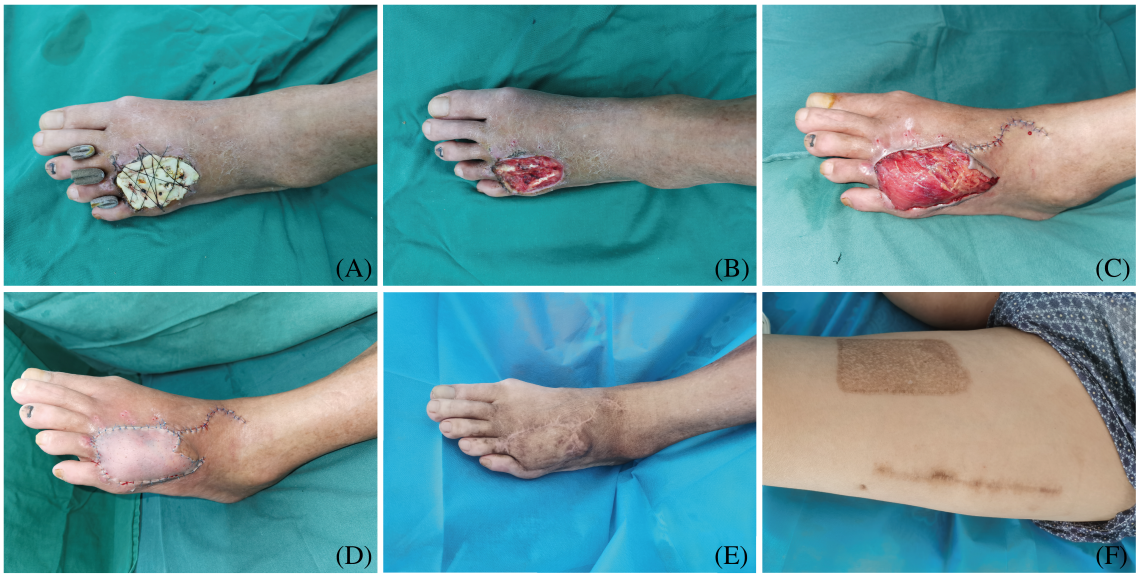

FIGURE 5 A 54-year-old male had diabetes and dorsum DFU on the left foot. (A) After stage I debridement, the wound was covered with bone cement. (B) During stage II, after ALBC's removal and tendon exposure, the formation of an 'induction membrane' could be seen. (C) A free VLMS flap was used to cover the wound. (D) The thigh STSG was used to cover the muscle. (E) At the 12-month postoperative follow-up, the flap showed a full and soft appearance. (F) The donor site scar was minor and easily concealed.

we are concerned that local muscle flap reconstruction for DFUs may damage the foot's blood supply, especially in patients with ischaemic DFUs. Also, we worry that this secondary injury may worsen foot neuropathy and impair foot function.

Free muscle flaps do not require secondary damage to the lower legs and feet and can achieve results equivalent to or better than those of local muscle flaps.[15,29] In 1991, Lai et al.[40] reported the successful reconstruction of 10 DFU cases using free gracilis flaps combined with

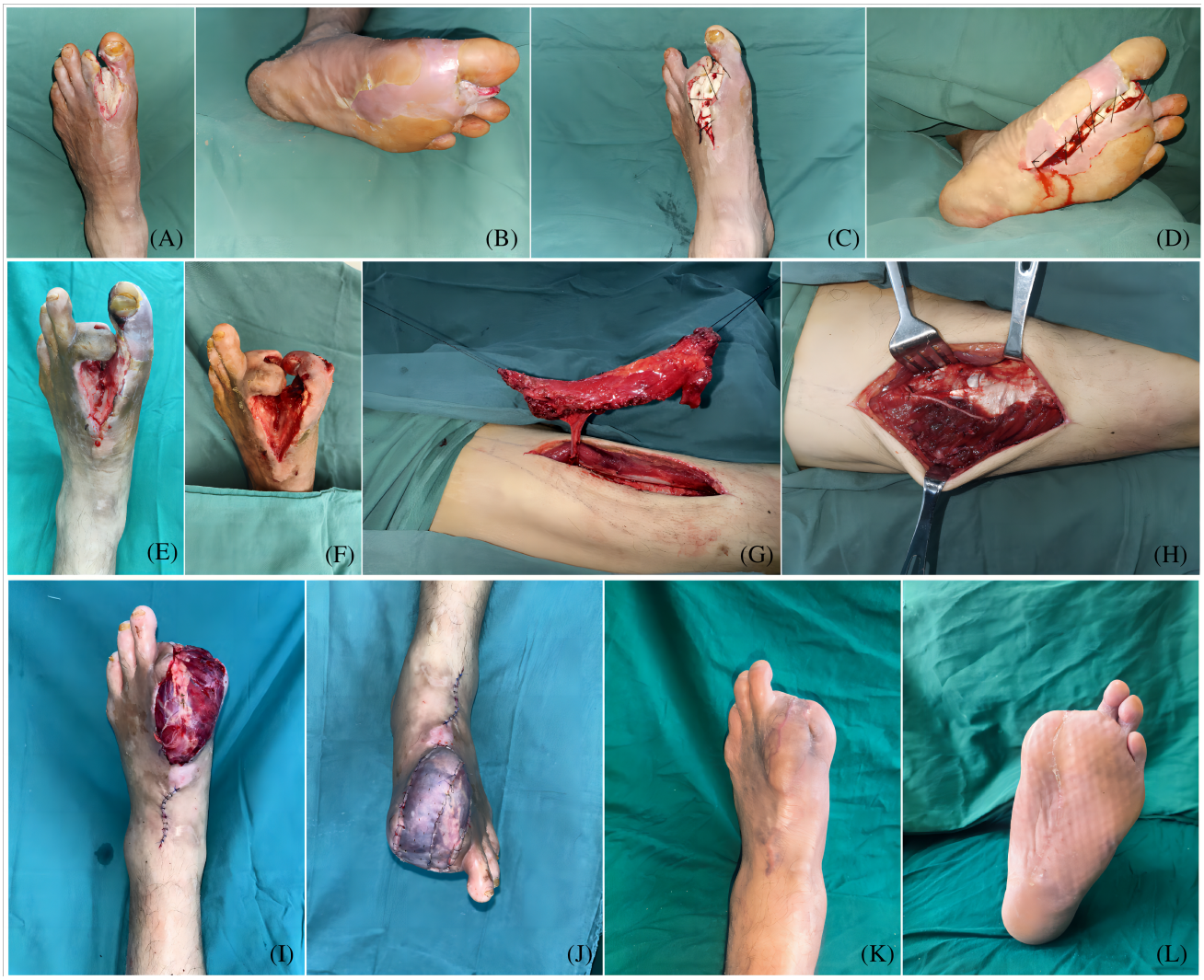

FIGURE 6 A 44-year-old male with diabetes and intermetatarsal DFUs on the left foot. (A, B) Photographs of the patient's foot before ALBC treatment. (C, D) After stage I debridement, the wound was covered with ALBC. (E) During stage II, after ALBC's removal, necrosis of the first toe and an induction membrane formation could be seen. (F) Picture of the wound after amputating the first toe. (G) Photograph before pedicle removal of the VLMS flap. (H) Parts of the superficial and intermediate partitions and the whole deep partition of the VLMS were preserved, as was the neuromuscular branch of the vastus lateralis nerve. (I) The free VLMS flap was used to cover the wound. (J) A scalp STSG was used to cover the muscle. (K, L) At the 24-month postoperative follow-up, the flap showed a smooth appearance.

STSGs. They believed that limb salvage could be achieved through this method. In a systematic review of the upshots of free tissue transfers in non-traumatic lower limb wounds of diabetic patients, the total free muscle flap combined with skin graft was 63%.[15] Currently, free muscle flaps such as rectus abdominis, latissimus dorsi, tensor fasciae latae, vastus lateralis, gracilis and serratus anterior have been reported for DFU reconstruction, with latissimus dorsi, gracilis and rectus abdominis being the most commonly used ones.[15,29] DFUs often involve bone defects, infections and necrotic cavities, which entail a considerable risk of amputation. Although chimeric flaps can be used to reconstruct DFUs with dead cavities,[41] the repaired skin grafts often become bulky and require secondary surgery for debulking, with the risk of damaging the cutaneous nerves during flap harvesting. Free muscle flaps have advantages such as shorter operation time, sufficient size, ability to fill dead cavities, abundant blood supply, strong anti-infection capabilities, good contour appearance and no damage to cutaneous nerves.[17,42,43] Therefore, combining free muscle flaps with STSGs may be an ideal choice for DFU reconstruction. Mayr-Riedler et al.[44] found that the risk of significant complications in reconstructing the forefoot using free fasciocutaneous flaps is four times higher than that of free muscle flaps, especially in elderly patients with ischaemic defects. Therefore, they recommended using free muscle flaps as the first choice for patients at higher

risk of complications. Czerny et al.[45] conducted a study showing that free muscle flaps combined with vascular reconstruction for lower limb ischaemic DFUs are workable. They found that the survival rate was 85%, the patency rate was 77%, and after an average follow-up of 51 months 70% of patients had regained the full function of their lower limbs. Hence, this approach allows for limb salvage, reduces mortality rates and provides good long-term results about graft patency and functionality.

The VLM is one of the four muscles in the anterior compartment of the quadriceps femoris muscle, and the selective harvesting of a muscle part does not affect knee joint function.[46,47] Compared to other free muscle flaps (more commonly used ones, such as latissimus dorsi, gracilis and rectus abdominis), the VLMS flap has the following advantages[17,46–48]: (*i*) easy harvesting in the supine position without requiring the patient to change position during surgery; (*ii*) tension-free or negative tension closure of the donor site after muscle flap harvest, resulting in a minimal scarring that can be well hidden; (*iii*) flexible design as the VLMS has a relatively large size (up to 20 × 12 cm) with no or low donor-site morbidity, allowing it to adapt to the volumetric reconstruction of the small to medium-sized defects; (*iv*) long vascular pedicle (18–20 cm) with large-calibre vessels (artery: 2.0–2.5 mm, vein: 2.5–4.0 mm), maximizing the length of the vascular pedicle by harvesting the distal portion of the muscle[46–48]; (*v*) minimal variation in vascular anatomy hence requiring no extensive intramuscular vascular dissection[47] and (*vi*) intact function of the donor site, as a longitudinal portion of the muscle is harvested, allowing to preserve its nerves with minimal or no impact on knee joint function.[46,47] Therefore, when a medium- to small-size flap with a long and sizeable vascular pedicle is needed, the vastus lateralis muscle flap should be considered as the preferred choice. Jiga et al.[17] used the VLMS flap combined with an STSG to reconstruct six cases of weight-bearing DFUs, and the foot function was significantly improved. These authors believed that their method is a safe and effective approach to cover weight-bearing areas, providing best cushioning and functional outcomes without concerns about complications at the donor site. However, there were two cases of partial loss of the STSGs, and more detailed reports on this topic are lacking. Moreover, the study by Mayr-Riedler et al.[44] showed that for every 1-minute increase in surgical time, there is a relative 1% increase in the risk of major surgical complications (total or partial loss of >10% of flap tissue and secondary surgery). Demirtas et al.[49] compared the clinical outcomes of free muscle flaps (including the rectus abdominis, latissimus dorsi and gracilis) with anterolateral thigh perforator flaps in reconstructing foot and ankle defects. They found that the surgical time for perforator flaps (352 ± 116 min) was significantly longer than that for free muscle flaps (240 ± 82 min). The incidence of complications was also significantly higher than for free muscle flaps. In our case series, the average surgical time was 156.9 ± 15.08 min (ranging from 135 to 186 min), which is lower than the time reported by Demirtas et al.[49] Moreover, with the denervation and the pressure on the muscle flap, the muscle flap gradually shrinks, and in the long term, it will not be bloated and hence does not need to be thinned. Thus, using free VLMS flaps combined with STSGs reconstruction for non-weight-bearing DFUs is a safe and dependable treatment, with potential benefits, such as the reduction of surgical complications.

We have learned the following lessons when applying this treatment strategy at our Center. Firstly, a preoperative assessment of the patient's local and overall condition must be thoroughly conducted. We recommend MDT for perioperative management and the WSIT group for local wound management, with an early focus on rapid infection control. DFU treatment involves avoiding amputation, efficiently repairing and preventing ulcer recurrence. Therefore, DFU patients should be admitted to departments equipped with wound repair capabilities, as this can effectively avoid worsening the patient's overall condition due to local factors. Second, although research has shown that it can be used for the reconstruction of weight-bearing zone ulcers,[17] we emphasize that the combination of free VLMS flaps and STSGs is suitable for the rebuilding of non-weight-bearing zone DFUs due to the lack of superficial sensibility. Thirdly, after reperfusion, the muscle flap tends to have a larger volume than before its pedicle is cut. We recommend that the length and width of the flap be 8% to 10% larger than the wound, while the thickness can be equal to or about 5%–10% thinner than the depth of the cavity or defect. Lastly, the successful reconstruction of a DFU does not imply its definitive cure. Such patients should be considered high-risk, and their medical education should be improved. It is essential to pay attention to signs such as calluses, blisters or bleeding and promptly address them, as these are the most important predictive factors for ulcer recurrence.[50,51] Customizing appropriate therapeutic shoes is also an essential measure to prevent recurrence. Multiple clinical trials have confirmed that proper protective footwear can reduce the occurrence and recurrence of ulcers.[52–54] Hashimoto et al.[55] also strongly recommend custom-made footwear for such patients, which is crucial for protecting the feet after free flap surgery and for preventing DFU recurrence.

The primary constraining limitation of this study is that it is a retrospective case series with a small sample size that lacks a control group. However, preliminary

results show that combining ALBC and VLMS flap with STSG is a reliable method for reconstructing pressure-free DFUs. Early follow-up results also suggested improvements in patients' QOL and foot function. Additionally, we lack precise quantitative metrics to evaluate muscular atrophy size, thus offering more correct guidance for selecting muscular volume to achieve the best contour of the foot. Another notable constraint lies in the abbreviated follow-up duration, precluding an assessment of enduring effects on DFUs of the ALBC-assisted VLMS flaps with STSGs reconstruction, including its implications for patients' amputation and survival rates. A commitment to ongoing patient monitoring is in place, with the anticipation of reporting comprehensive, long-term outcomes in later research endeavours.

5 | CONCLUSION

Based on WSIT mode, an ALBC-based combination of free VLMS flap and STSG is a reliable strategy for reconstructing non-weight-bearing area DFUs. This strategy effectively controls infection and improves QOL and foot function while reducing hospitalization time. Although this is a retrospective case series, due to the many advantages of this approach, we strongly recommend incorporating this strategy into the treatment plan for non-weight-bearing area DFUs.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University (No. KLL-2023-518). The patients/participants provided written informed consent to take part in this study. Written informed consent was obtained from the individual(s) to publish any potentially identifiable images or data in this article.

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