Real-world outcomes of autologous whole blood clot therapy for venous leg ulcers

Objective: Venous leg ulcers (VLUs) are hard-to-heal wounds primarily caused by venous insufficiency and venous hypertension. These wounds pose significant clinical and economic burdens, often failing to heal with standard compression therapy alone. Autologous whole blood clot (AWBC) therapy has emerged as a potential treatment for hard-to-heal wounds, complementing the body's natural wound healing mechanisms. This study aims to evaluate the outcomes of AWBC in a real-world setting for treating VLUs that have not responded to conventional therapies.

Method: A multicentre observational registry study was conducted between August 2021 and December 2024 (NCT04699305) across multiple countries. Patients with hard-to-heal VLUs were included to receive AWBC application. Median wound duration at baseline was 13.5 months (interquartile range: 5.25, 36.0). AWBC applications were used alongside compression therapy, and outcomes were assessed in terms of percentage area reduction (PAR) and complete wound healing.

Results: There were 56 patients in the study cohort. AWBC treatment resulted in a mean wound area reduction of 71.3%. Complete healing was achieved in 45% of patients, while 54% exhibited a PAR >90%. Among the wounds treated, 44% that had persisted for >1 year achieved complete healing. Treatment duration varied, with some patients requiring extended therapy (12–20 weeks) to achieve significant wound progression. Adverse events were minimal and unrelated to treatment.

Conclusion: In this study, AWBC therapy demonstrated high levels of effectiveness in treating hard-to-heal VLUs, particularly in patients whose wounds had failed to heal with standard compression therapy. AWBC therapy provides a supportive extracellular matrix, modulating inflammation and enhancing wound healing, demonstrating its valuable conjunction treatment to existing compression treatment protocols.

Declaration of interest: During the preparation of this manuscript, Grammarly (Grammarly Inc., US) was used to assist with spelling and grammar checks. No artificial intelligence tools were used for content generation or data analysis. SH and RS are consultants for RedDress Medical, FL, US. The other authors have no conflicts of interest to declare.

autologous whole blood clot • extracellular matrix • hard-to-heal • treatment • venous hypertension • venous insufficiency • venous leg ulcers • wound • wound care • wound dressing • wound healing

Venous leg ulcers (VLUs) are the most common type of hard-to-heal lower extremity wounds, accounting for 60–80% of lower extremity ulcers,[1,2] with prevalence increasing with age and more common in females.[2,3] The economic burden of VLUs is significant, accounting for an estimated 1–2% of the annual healthcare budget in Europe, and costing between $2.5–14.9 billion USD annually in the US.[4,5] The effect on the patient is significant: VLUs are usually painful and prone to infections, severely impacting the patient's mobility and quality of life.[6] The main cause of VLUs is complications of venous disease, such as venous hypertension and venous insufficiency.[3] Venous hypertension may impair oxygen and nutrient exchange;[7] downregulate fibrinogen synthesis leading to inadequate collagen production; and reduce capillary perfusion,[7,8] causing erythrocyte aggregation, leukocyte plugging and ischaemia.[7–9] Leukocytes also release inflammatory mediators, cytokines and free radicals that damage vascular structures and increase permeability.[10,11]

Compression therapy remains the cornerstone of VLU treatment, aiming to counteract the increased hydrostatic pressure caused by chronic venous insufficiency, and therefore to increase venous return.[12,13] Nevertheless, adjunctive treatments are often necessary to achieve complete healing, especially in cases where compression fails to cause the wound to progress, which occurs in 33–66% of ulcers.[13] Failure to demonstrate progress after six weeks of compression is generally considered an indication of treatment failure.[14] In 15–30% of cases, the wound remains unhealed after one year, emphasising the need for earlier intervention with adjunctive therapies.[15] For these wounds, delaying the initiation of alternative therapies to improve patient outcomes may increase the risk of ulcer recurrence and result in higher treatment costs.[16]

Autologous whole blood clot (AWBC) is a bedside treatment using the patient's own blood to create a topical blood clot dressing. AWBC is a US Food and Drug Administration and CE-approved product, and was found to be safe and effective in treating cutaneous wounds. AWBC efficacy has been previously demonstrated in several clinical and registry trials involving patients with diabetic foot ulcers (DFUs),

https://doi.org/10.12968/jowc.2025.0419

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pressure ulcers (PUs), and surgical and complex wounds.[17–23]

The mechanism of action of AWBC is attributed to its extracellular matrix (ECM)-like properties, which provide both a mechanical barrier and a supportive environment that promotes the wound healing process.[24] By creating a mechanical barrier, AWBC helps prevent bacterial bioburden and protects against wound deterioration. The platelets in the blood clot participate in the formation of neutrophilic extracellular traps by adhering to neutrophils, which aid in bacterial clearance.[25,26] The fibrin matrix created facilitates tissue repair, leukocyte adhesion and endothelial cell migration during angiogenesis.[27] The plethora of cells within the clot plays a crucial role in the wound healing cascade by secreting cytokines and chemokines into the wound microenvironment, resulting in an anti-inflammatory effect. By modulating local immune responses and introducing regenerative signalling molecules, AWBC facilitates the healing process and enables the wound to progress beyond its stagnant stage.[24]

In this study, the outcome of using AWBC as a treatment for VLUs in patients who had failed conventional treatment for their ulcer was evaluated.

Method

This was a multicentre, retrospective, observational study, using patient data collected from a registry database from August 2021 through to December 2024 (ClinicalTrials.gov registered study: NCT04699305). This study aimed to evaluate the outcomes of AWBC in a real-world setting among patients with VLUs who, in the opinion of their wound care specialists, were unresponsive or showed insufficient progress following compression therapy combined with conventional standard of care (SoC) treatment. Being an observational study, the mode of treatment and the choice of compression therapy were not standardised among patients.

The registry included patients with complex or hard-to-heal wounds treated with AWBC across multiple outpatient and wound care settings. Data were collected prospectively at each treatment visit, including wound measurements, photographs and clinical notes, and were compiled into a central database for analysis. Given the retrospective observational design of the study and the diversity in patient characteristics, wound profiles and treatment regimens, no inferential statistical testing or adjustment for confounders was performed. Analysis was limited to descriptive statistics to represent the outcomes observed in routine clinical practice without introducing bias from inappropriate statistical assumptions.

Patients

Patients were enrolled from participating sites in the US, Israel, Turkey and South Africa. Patients were treated in both public and private healthcare sectors. Inclusion criteria required participants to be ≥18 years of age, to present with a VLU, and to be able to provide informed consent. Patients were not excluded based on their comorbidities or wound characteristics. Those with wound infections received treatment to control the infection prior to initiating AWBC therapy.

Ethical approval and patient consent

AWBC is an approved and commercially distributed

Fig 1. Autologous whole blood clot preparation. Drawing 18ml of patient blood into an acid citrate dextrose adenine (ACDA) tube **(a)**. Puncturing the coagulation mould, which contains calcium gluconate and kaolin powders, using a designated punch tool to create an air outlet **(b)**. Withdrawing blood from the ACDA tube into a 20ml syringe and injecting it into the coagulation mould **(c)**. Sealing the coagulation mould and mixing the blood with the coagulation agents by gently shaking and turning the mould for 20 seconds **(d)**. Allowing the blood to coagulate for approximately 5–8 minutes, then gently opening the backing and loosening the clot **(e)**. Placing the clot on the wound, securing it with Steri-Strips, and covering it with a secondary dressing **(f)**

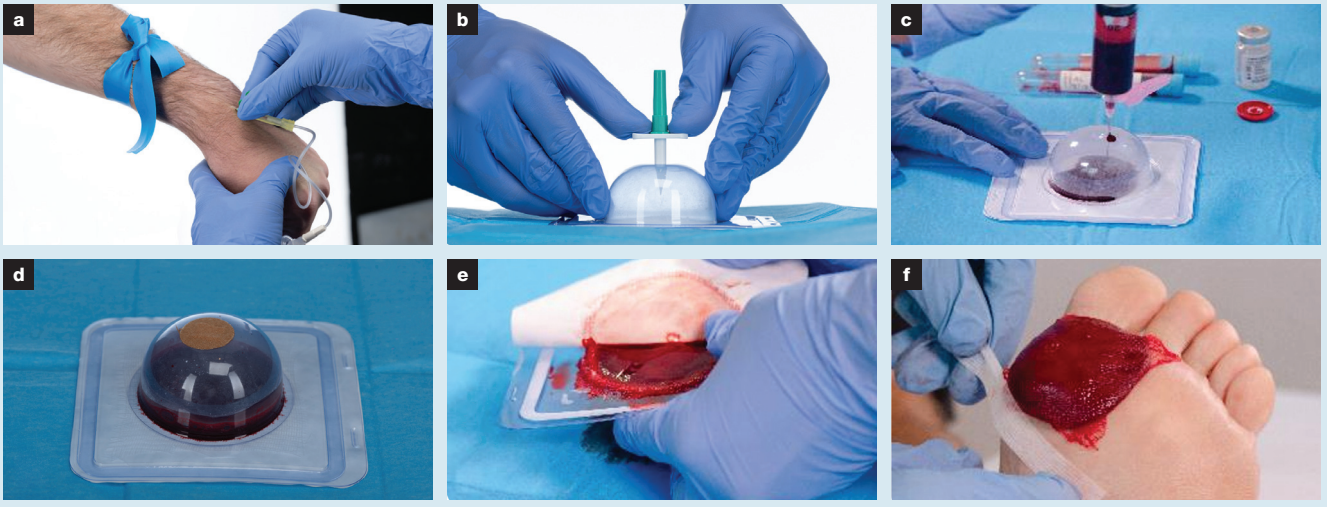


Table 1. Patient baseline characteristics

Variable	Value
Age, years, mean (±SD)	69.9±11.4
Sex, n (%)	
Female	22 (39)
Male	34 (61)
Multiple comorbidities, n (%)	38 (68)
Diabetes status, n (%)	16 (27)
Wound size at baseline, cm², median (IQR)	8.96 (2.24, 18.62)
Wound duration, months, median (IQR)	13.5 (5.25, 36.0)
Wound duration >1 year, n (%)	27 (48)

IQR—interquartile range; SD—standard deviation

product for the treatment of cutaneous wounds in all countries where data was collected. Its clinical use in this study was consistent with routine medical practice and in accordance with local regulations and, therefore, additional ethical approval was not required.

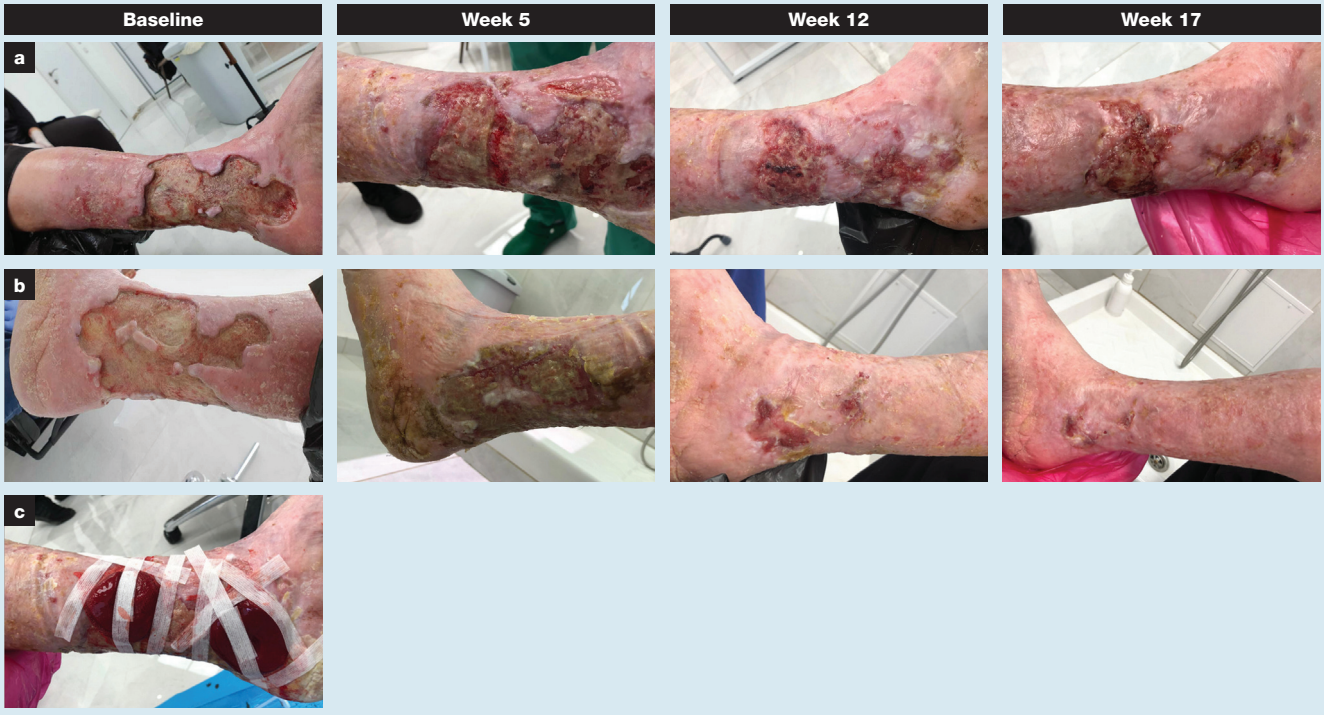
All patients signed informed consent allowing the use of their demographic data, wound properties and wound images without the involvement of a legal authorised representative.

Wound edge preparation and AWBC application

Prior to AWBC application, debridement was performed as required to remove all non-viable or necrotic tissue, based on wound characteristics and clinical judgement. Cleansing, bacterial bioburden assessment and moisture management were completed before each AWBC application. The methods chosen for debridement, cleansing and assessment of bacterial bioburden were not standardised, and were based on the discretion of the investigator, reflecting real-world practice.

AWBC was prepared following the manufacturer's protocol. Briefly, 18ml of the patient's blood was collected into acid citrate dextrose adenine vacuum tubes. The blood was gently mixed with calcium coagulant and kaolin within a coagulation mould to produce a 28cm² blood clot, which formed in approximately 5–8 minutes. The clot was then placed on the wound and secured using Steri-Strips attached to clot-embedded gauze to maintain stability. The clot was covered with a non-adherent dressing and foam, followed by layers of gauze to absorb any fluids exuding from the clot (Fig 1). The secondary dressing (outer foam and gauze) was changed by the patient after 2–3 days, depending on the amount of exudate, to maintain a dry wound environment. AWBC was reapplied weekly at the investigator's discretion. Treatment with AWBC was supplemented with SoC compression therapy, as determined by the investigator. The wounds were

Fig 2. Case 1: an 87-year-old male patient, with a medical history of venous insufficiency and venous hypertension, presented with a venous leg ulcer of seven years' duration, located on the medial **(a)** and posterior calf **(b)** of the right leg. The wound was treated with autologous whole blood clot (AWBC) for a total of 16 applications. The wound, which initially measured 247cm², achieved a 94% reduction in area following treatment with AWBC **(a,b)**. Due to its large size, two clots were placed on the wound, covering the majority of the affected area **(c)**



followed up weekly to assess progress. Wounds that showed no progress after four weeks of treatment were deemed non-responsive and subsequently discontinued from the study.

Safety outcomes

Safety data were collected from all patients, and safety was evaluated by the overall incidence and severity of adverse events (AEs), based on Common Terminology Criteria for Adverse Events, version 5.[28]

Data collection and analysis

Baseline data were collected and extracted from the patient's medical records, including the patient's demographics, medical history, wound profile and past treatments, along with measurements and wound images. Statistical analyses included descriptive summaries of demographics and wound baseline characteristics. Outcomes were assessed by calculating the percentage area reduction (PAR) for each wound, as well as the overall PAR across all wounds.

Results

This study included 56 patients who were treated with AWBC. The mean age of the cohort was 69.9±11.4 years (95% confidence intervals (CI): 65.78, 73.74), comprising 22 female patients and 34 male patients. Of the included patients, 16 had diabetes and 40 did not, with the majority having multiple comorbidities, and 27 (48%) having wounds that had persisted for >1 year. The median wound duration was 13.5 months (interquartile range (IQR): 5.25, 36.00) with median wound size at baseline of 8.96cm^2 (IQR: 2.24, 18.62) (Table 1).

AWBC treatment was applied for an average duration of 8.3±4.8 weeks (range: 1–21 weeks; 95% CI: 7.00, 9.65), resulting in an overall PAR of 71.3%. Complete healing (full re-epithelialisation) was achieved in 25 (45%) patients, while 30 (54%) patients experienced a PAR >90%. Complete healing was achieved by 12 (44%) patients with an ulcer duration of >1 year, using AWBC treatment. It is worth noting that seven (13%) patients received >12 applications (mean: 15.6 applications), achieving a PAR of 70.6%. The treatment duration and number of applications were determined by the wound care specialists based on observed improvements and the effectiveness of the treatment regimen.

In a subgroup analysis by diabetes status, no significant differences were observed between patients with diabetes and those without. The PAR was 75.87±39.2% in patients with diabetes and 70.16±36.4% in those without. Similarly, when analysed by wound size (<5cm^2, 5–10cm^2 and >10cm^2), no statistically significant differences were found. The number of wounds in each category was 25, 6 and 21, respectively, with corresponding PAR values of 69.32±39.57%, 71.17±31.69% and 67.6 ±38.80%, respectively.

Treatment was discontinued by 15 patients during the study for the following reasons: insufficient treatment efficacy (treatment failure) (n=6); inability to withdraw blood for the application (n=2); infection (n=3); serious AEs (SAEs, n=2); loss of insurance coverage (n=1); and patient non-adherence (n=1). The discontinued patients were included in all statistical analyses, including efficacy, with their outcomes assessed based on the data collected at their final visit and wound measurement.

In this study, the safety of AWBC treatment was

Fig 3. Case 2: an 80-year-old female with multiple comorbidities, including venous insufficiency and venous hypertension, presented with a painful venous leg ulcer of 36 months' duration, which had failed to heal with conventional therapy. The wound, measuring 10.84cm^2, was treated with autologous whole blood clot for a total of six applications over the course of 12 weeks, achieving complete wound closure

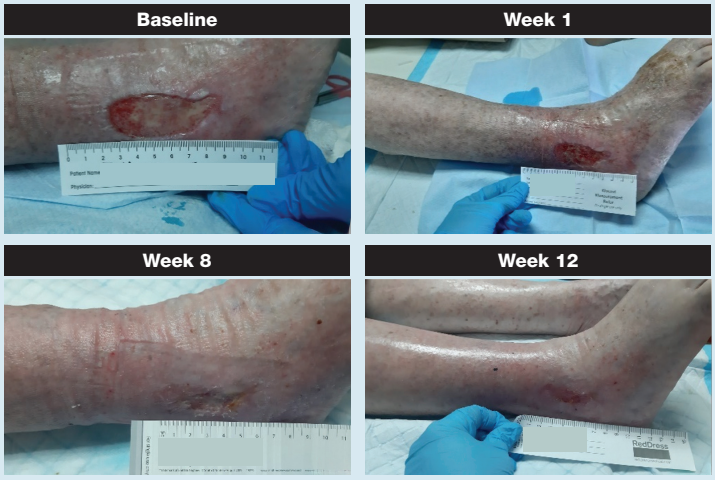
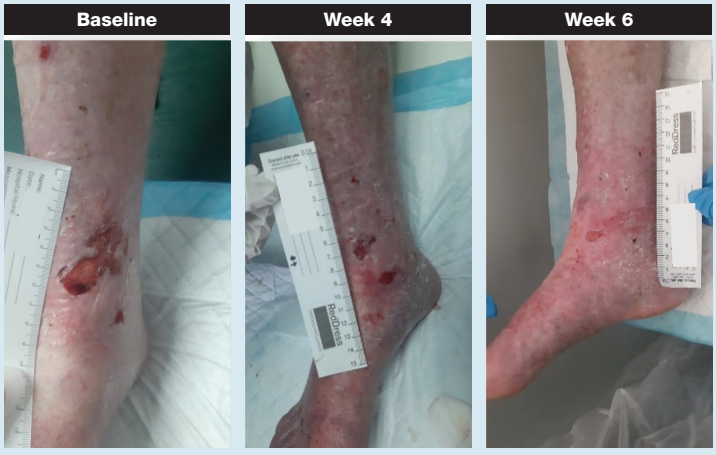


Fig 4. Case 3: a 69-year-old female patient presented with a venous leg ulcer of 24 months' duration on her right leg. Medical history included diabetes, peripheral artery disease, venous insufficiency, venous hypertension, peripheral neuropathy, deep vein thrombosis, Guillain-Barré syndrome and immune deficiency. The wound had failed multiple previous treatments at healing and was subsequently treated with autologous whole blood clot therapy for four consecutive weeks, resulting in an 88% reduction in wound area. Complete closure was achieved by week 6 with continuation of standard of care



assessed by monitoring the AEs and SAEs reported throughout the treatment period. Of the three reported infections, two occurred in the treated ulcer, while one was located on the thigh of the treated leg. In all, two SAEs were observed: one patient was diagnosed with stage 4 stomach cancer, and the other experienced significant blood loss due to a scratch from a house pet. All the AEs were classified as not being related to the treatment.

Representative cases demonstrating AWBC treatment outcomes are shown in Figs 2–4.

Case 1

An 87-year-old male patient with venous insufficiency and hypertension presented with a seven-year VLU (wound size: 247cm²) on the right calf, previously unresponsive to ozone therapy, dressings and compression therapy. Over a period of four months, 16 AWBC applications resulted in a 94% wound size reduction (Fig 2).

Case 2

An 80-year-old female patient with multiple comorbidities, including diabetes, venous insufficiency, venous hypertension, peripheral neuropathy, deep vein thrombosis, Guillain-Barré syndrome and immune deficiency, had a 36-month VLU (wound size: 10.84cm²) resistant to silver sulfadiazine, honey and compression therapy. Over a period of eight weeks, six AWBC applications led to complete healing and pain reduction (Fig 3).

Case 3

A 69-year-old female patient with extensive comorbidities presented with a VLU of 24 months' duration (wound size: 13.19cm²) on the medial leg. After four AWBC applications, the wound size reduced by 88% (to 1.57cm²) within four weeks, followed by complete closure after an additional two weeks of SoC (Fig 4).

Discussion

The treatment of VLUs in patients whose wounds fail to progress with compression therapy poses a challenge in wound management, creating a growing financial burden on the health system, which is expected to increase with the ageing population.[29] Treatment options are limited and there remains an unmet need for more advanced technologies capable of taking wounds from their stagnant stage toward healing.

This study was conducted as an observational study in cases of VLU, assessing real-world outcomes. The treated wounds were hard-to-heal, with a mean duration of 34.4±61.2 months, and 48% persisted for >1 year. It is noteworthy that the baseline wound area was 2–3-times larger than those typically reported in clinical studies.[30,31] Despite this, AWBC demonstrated a strong therapeutic effect, achieving an overall PAR of 71.3%, with 45% of the wounds reaching complete healing. Subgroup analysis showed that wound healing outcomes were not significantly affected by either diabetes status (patients with diabetes versus patients without) or wound size (<5cm², 5–10cm² and >10cm²). No major differences in baseline characteristics were observed between these groups. Among the treated patients, 15 discontinued treatment and withdrew from further participation. The most common reason was treatment insufficiency (n=6). In these cases, treatment was stopped when no signs of improvement were observed after four AWBC applications, and patients were referred to alternative treatment options. These discontinuations reflect the realities of a real-world clinical practice, where not all patients are suitable candidates for every therapy and external factors, such as comorbidities, technical feasibility and socioeconomic barriers, play a role in treatment adherence. The results of this current study support the potential therapeutic effect of AWBC in hard-to-heal wounds, with the present cohort demonstrating meaningful wound area reduction and complete healing outcomes in patients with VLUs.

The previously reported mechanism of action for AWBC suggests that the ECM-like properties of AWBC help create a supportive wound environment by regulating cellular activity through dynamic reciprocity, which is essential for tissue repair.[32] In the hard-to-heal wound, excessive secretion of matrix metalloproteases (MMP-2, MMP-8, MMP-9) and human neutrophil elastase leads to ECM degradation.[33,34] By acting as a protective scaffold, AWBC is suggested to improve cellular communication and help restore balance to the wound environment, potentially enabling progression from the inflammatory phase toward tissue repair.[24]

Interestingly, the stagnant inflammatory stage of the wound is also attributed to the proinflammatory phase of the surrounding macrophages, which play a crucial role in wound healing. During the inflammatory phase, macrophages polarise into M1 (proinflammatory) and M2 (anti-inflammatory) phenotypes, with M1 macrophages promoting initial immune responses and M2 macrophages facilitating tissue repair through anti-inflammatory cytokines and proangiogenic factors.[35] In acute wounds, macrophage plasticity allows the transition from M1 to M2; however, in hard-to-heal wounds, the M1 macrophage dominance keeps the wound in the inflammatory phase. Interestingly, both DFUs and VLUs contain a significantly higher number of macrophages compared with acute wounds, suggesting their critical role in the pathophysiology of these hard-to-heal wounds. It was suggested that AWBC can suppress this phenotype and promote polarisation toward the M2 phenotype.[35] By collaborating with fibroblasts during matrix remodelling, the M2 macrophages contribute to cytokine secretion and ECM regulation, promoting the healing cascade out of the stagnant inflammatory phase.[36]

The AWBC's cellular and molecular components, which include leukocytes, neutrophils and monocytes,

may also contribute to the observed outcomes by supporting pathogen clearance and enhancing local immune responses.[24] The embedded neutrophils within the matrix release molecules, such as defensins and cathelicidins, which exhibit strong antimicrobial effects, helping to inhibit bacterial growth and reduce the risk of infection.[37] The contained monocytes differentiate into macrophages, which secrete interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), enhancing the local immune response.[35] This suggested synergic effect of AWBC in reducing the risk of infection while promoting wound healing highlights its unique therapeutic potential.

Limitations

This study was based on real-world data from a registry trial, which presents several limitations. Due to coverage constraints, most patients were not treated until complete wound closure, but, rather, until sufficient wound progression was achieved. As a result, the true rate of complete healing may be under-represented. Additionally, the type of compression used, treatment regimens and dosing were not standardised, as they were determined at the discretion of the investigators. This variability in frequency, duration and application techniques may have influenced outcomes and introduced potential confounding factors.

Furthermore, registry studies lack the controlled conditions of a randomised controlled trial (RCT), making it difficult to eliminate external factors that may have impacted wound healing, such as patient comorbidities, adherence to treatment and concurrent therapies. Moreover, the lack of a comparator group (e.g., compression therapy alone), makes it difficult to distinguish whether the improvements were solely due to AWBC treatment or to other factors.

Conclusions

The findings of this study demonstrate the outcomes of AWBC in a real-world setting as a treatment for VLUs in patients who failed to progress with conventional compression therapy. While the absence of a comparator group limits causal interpretation, the prospective design and diverse patient population strengthen the reliability and applicability of the findings. Despite the hard-to-heal nature and large baseline wound size of the ulcers, AWBC treatment was associated with significant wound size reduction, with a notable percentage of patients achieving complete healing. Moreover, registry-based real-world studies such as this offer unique insight by capturing outcomes across a wide spectrum of patients, comorbidities and wound characteristics that are often excluded from randomised trials, thereby increasing external validity. The systematic, prospective data collection reflects routine clinical practice rather than the controlled environment of an RCT. This study provides valuable insights into how AWBC performs in everyday practice and across heterogeneous clinical settings. These results suggest that AWBC may serve as a promising adjunctive therapy for hard-to-heal wounds, potentially providing a supportive ECM-like environment that promotes wound healing and which may help reduce infection risks. Controlled, prospective studies are needed to confirm these findings. JWC

Reflective questions

- What are the main challenges in treating venous leg ulcers (VLUs) that fail to progress with standard compression therapy, and how does autologous whole blood clot (AWBC) therapy address these challenges?
- How does the mechanism of action of AWBC differ from traditional therapies, and what implications does this have for wound healing outcomes?
- In what ways could earlier use of AWBC in VLUs potentially improve patients' outcomes, reduce recurrence and healthcare costs?
- Based on the findings of this study, what additional evidence would be most valuable in guiding future clinical adoption of AWBC therapy for VLUs?

Funding statement
RedDress Ltd., FL, US, the manufacturer of the AWBC device, provided the kits used in the study.

Acknowledgment
The authors would like to thank Shira Cohen for her assistance in writing this manuscript.

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