Efficacy of a dual-layer pre-hydrated amniotic membrane allograft in the treatment of hard-to-heal wounds

Objective: Hard-to-heal wounds refractory to standard of care (SoC) therapy pose a major clinical and economic burden on healthcare systems. A dual-layer hydrated human amniotic membrane (HAMA) allograft, pre-hydrated with saline, is an emerging advanced therapy for complex hard-to-heal wounds. The aim of this study was to evaluate the real-world effectiveness of Membrane Wrap Hydro (BioLab Holdings, Inc., US) in achieving complete closure and relative percentage area reduction (PAR) across hard-to-heal diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), pressure injuries (PIs) and open wounds.

Method: This was a retrospective multicentre analysis of patients treated from November 2024 to July 2025 after ≥30 days of optimised SoC with <50% healing. Weekly applications of HAMA were performed in outpatient clinics, nursing homes or home settings. The primary endpoint was complete wound closure (99.99–100% re-epithelialisation). Secondary endpoints were: PAR (paired samples t-test); applications to closure; and time-to-healing (Kaplan–Meier).

Results: The cohort included 80 patients (83 wounds). Complete closure occurred in 46/83 (55.4%) wounds with a median six applications (mean: 6.54±3.22). Closure rates were: 53.3% (DFUs); 50.0% (VLUs); 47.1% (PIs); and 59.6% (open wounds). Mean PAR was 84.3%, with significant area reduction from baseline ($p<0.001$; Cohen's $d=0.79$). Large effect sizes were observed across aetiologies ($d=1.01–1.84$). Median time-to-healing was 42 days (range: 7–110).

Conclusion: Membrane Wrap Hydro achieved clinically meaningful closure and substantial PAR across diverse refractory hard-to-heal wounds, with outcomes in PIs and open wounds comparable or superior to DFUs and VLUs. These findings support the role of HAMA as a versatile advanced therapy in multimodal hard-to-heal wound management.

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advanced wound therapy • chronic wound • hard-to-heal wound • hydrated amniotic membrane allograft • percentage area reduction • real-world evidence • wound • wound care • wound dressing • wound healing

The use of cellular, acellular and matrix-like products (CAMPs), particularly from human amnion, has garnered significant attention for the treatment of hard-to-heal wounds, notably diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs). Current research emphasises the multifaceted properties of amniotic membranes, which include compositions of growth factors, cytokines and extracellular matrix (ECM) components that are crucial for promoting wound healing.

Clinical trials[1,2] have demonstrated the efficacy of amniotic grafts in the management of hard-to-heal wounds. The use of amniotic membranes accelerates healing compared to standard of care (SoC) options in patients with DFUs, thereby supporting the clinical application of these grafts for treating hard-to-heal wounds.[1,2] Supporting literature has shown that patients treated with amniotic grafts exhibited significant improvements in wound healing outcomes in multicentre randomised controlled trials (RCTs).[3]

Pre-hydrated amniotic membrane has a unique composition that supports healing by providing a rich source of angiogenic growth factors, such as vascular endothelial growth factor and transforming growth factor-beta, as well as cytokines instrumental in wound healing processes.[4–8] Specifically, studies have shown that human amnion membrane allografts not only facilitate cell migration to the wound site but also aid in neovascularisation, which is vital in restoring the adequate blood supply necessary for healing.[4–7]

Amniotic grafts not only enhance healing rates, but also possess properties that mitigate pain and inflammation. The anti-inflammatory cytokines present within the grafts inhibit excessive scar formation and promote a more conducive healing environment.[8,9] Moreover, the role of mesenchymal stem cells has been shown to offer additional regenerative capabilities to augment the healing process when coupled with amniotic grafts.[9]

The safety and practicality of using amniotic products are also noteworthy. The use of aseptically processed amnion grafts has been shown to reduce infection rates

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while enhancing healing, making amniotic grafts a viable option in the management of hard-to-heal wounds where the risk of complications is significant.[10] Furthermore, dehydrated human amnion/chorion membrane has become widely accepted due to its stability, ease of application and effective integration into the wound bed, as evidenced by studies highlighting its success across various hard-to-heal wound types.

Dual-layer hydrated amniotic membrane allografts (HAMAs), pre-hydrated with saline, present a promising therapeutic approach for hard-to-heal wound management. Beyond their biological and mechanical properties that promote healing, ongoing research continues to refine our understanding of how these grafts can be effectively implemented in clinical settings to improve patient outcomes. The synergy between the bioactive compounds present in the amniotic tissue and patient-specific factors indicate that a multifactorial approach to hard-to-heal wound care may yield substantial benefits.[11]

The present retrospective analysis was undertaken to evaluate the real-world clinical effectiveness of Membrane Wrap Hydro (BioLab Holdings, Inc., US), a dual-layer HAMA, pre-hydrated with saline, in the treatment of complex, hard-to-heal wounds refractory to 30 days of SoC therapies. By analysing outcomes in a diverse cohort of patients with hard-to-heal DFUs, VLUs, pressure injuries (PIs) and other open wounds of various aetiologies, durations and severities, the authors aimed to assess complete wound closure rates, time to closure and reduction in wound area. Additionally, the study sought to provide practical insights into the role of this advanced amniotic allograft within multimodal hard-to-heal wound management protocols and contribute to the growing body of evidence supporting the use of human amniotic membrane products in all challenging wound aetiologies.

Methods

Data source and definitions

The electronic health record (EHR) database of a multicentre wound medicine private practice within Louisiana, Mississippi, Arkansas, Tennessee and Texas was used to review all patients who had received the Membrane Wrap Hydro, dual-layered amniotic membrane allograft. Data for the analysis were obtained from patients receiving an amniotic membrane allograft between 3 January 2018 and 31 July 2025. Patients receiving the HAMA graft were identified within the date range of 13 November 2024 and 31 July 2025. Wound treatment occurred in outpatient clinics, nursing home facilities and patients' homes. Accounts receivable reports (AR reports; financial documents providing a detailed overview on billing reports through specific codes) were obtained for identification of International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnosis codes and Current Procedural Terminology (CPT) codes.[12,13] Patient wound aetiologies included hard-to-heal DFUs, VLUs, PIs and open wounds. Wound aetiologies were also verified through AR reports documented in the EHR through ICD-10 and CPT codes. Lastly, wound characteristics and patient demographics were obtained by one investigator through manual chart review.

All patients included for analysis had completed 30 days of SoC before the initial application of the HAMA. These patients were noted to have <50% area reduction (PAR) of their wounds, further establishing the wounds analysed as hard-to-heal.[14] These patients also met the 2025 Local Coverage Determination (LCD) criteria established by Medicare Administrative Contractors (MACs) for hard-to-heal wounds to be eligible for the amniotic membrane allograft application.[15] An application series was defined as patients having received consecutive allograft applications, with no more than 21 days between applications, for up to a limit of 15 applications.

Hard-to-heal wounds were categorised into four types for this analysis. DFUs were characterised as full-thickness wounds located on the ankle or foot in patients with a confirmed diagnosis of diabetes (type 1 or 2). VLUs were defined as full-thickness wounds on the lower extremities in patients with a diagnosis of venous insufficiency, confirmed by a duplex ultrasound demonstrating venous reflux >0.5 seconds. PIs were defined as full-thickness wounds occurring over bony prominences or attributable to pressure from medical devices, regardless of anatomical location. Open wounds encompassed all other hard-to-heal, full-thickness wounds of varying aetiologies (trauma, surgical and 'other') and locations not meeting the criteria for DFUs, VLUs or PIs.

Wound surface area was measured using standardised ruler-based length × width methodology across all participating sites. The initial wound measurement was recorded at the first application of the HAMA. The final wound measurement was obtained at the last allograft application or within 14 days after the last graft application. Complete wound closure (healed) was defined as achieving of 99.99–100% PAR with full re-epithelialisation, as documented in the EHR. Parameters to classify healed percentages were required for consistency, given that clinicians (physicians, nurse practitioners and physician assistants) frequently recorded residual healed wound areas as 0.01cm^2 during ongoing patient follow-up. Patients with measurements of 0.01cm^2 continued follow-up at the discretion of the provider to ensure that the wound(s) remained closed until discharge from wound medicine services, as documented with a wound surface area of 0.0cm^2.

Ethical considerations

Institutional Review Board (IRB) approval for this study was granted by Sterling IRB (ID number: 15321; 4 December 2025).

Patient consent was gained before analysis, although this was not required by the IRB.

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Design and procedures

This retrospective analysis focused on patients with hard-to-heal wounds who underwent HAMA treatment. The primary objective of this analysis was to assess the efficacy of the HAMA for wound closure. The secondary objectives included an analysis of PAR in those wounds having received HAMA applications. Reimbursement for this allograft treatment adhered to local MAC guidelines throughout the study duration.

Wound medicine clinicians strictly adhered to the institutional protocols for the application of CAMPs, ensuring the HAMA was applied only after optimisation of SoC measures. This required a minimum four-week period of SoC that included surgical and/or ultrasonic debridement, confirmation of adequate perfusion, elimination of infection and necrotic tissue, and initiation of appropriate offloading or compression therapy. Optimal nutrition support was also assessed, with counselling and treatment provided as indicated. Smoking cessation counselling was offered when indicated, and patients with poorly controlled diabetes received targeted education, medication adjustments and referral to primary care or endocrinology, as needed.

Primary dressings were selected to secure the HAMA to the wound bed, while secondary dressings were used to manage exudate. Pressure relief and offloading strategies were individualised to patients according to wound aetiology and anatomical location. For plantar DFUs, total contact casts, therapeutic footwear or custom orthoses were used. Pelvic PIs were managed with pressure-redistribution mattresses, specialised wheelchair cushions and enforced sitting limit times, at the providers' discretion. Lower extremity PIs were managed with heel-offloading protection and orthotic cushions, as applicable. VLUs were treated with sustained compression therapy to reduce ambulatory venous hypertension.

Secondary dressings were changed 2–3 times weekly, depending on exudate amount, whereas the primary dressings and HAMA graft typically remained undisturbed for approximately seven days. Patients returned for weekly treatment visits, during which providers performed debridement as necessary and reapplication of the HAMA, continuing this cycle until the application series was complete or until full wound closure was achieved.

Outcome measures

The primary outcome for this retrospective analysis was to evaluate the rate of wounds achieving complete closure (healed with full re-epithelialisation) at the conclusion of treatment with the HAMA. Secondary endpoints comprised the average number of applications needed to achieve complete wound closure and the PAR observed after each application in hard-to-heal wound treatment. Baseline patient demographics were reported descriptively. Relevant comorbidities were identified through manual chart review, with emphasis on conditions commonly encountered in specialised wound management practice settings.

Sample selection

A dataset was compiled by identifying patients who received CAMP applications between 3 January 2018 and 31 July 2025. CPT codes were employed to select patients who had exclusively received the Membrane Wrap Hydro allograft between 13 November 2024 and 31 July 2025. ICD-10 diagnosis codes were then used to identify patients with wounds arising from aetiologies including DFUs, VLUs, PIs and open wounds. To ensure adherence to the predefined application series, patients exhibiting intervals >21 days between consecutive applications were excluded from the analysis. Additionally, patients diagnosed with connective tissue diseases were evaluated to ascertain whether these conditions affected healing within cutaneous tissues (e.g., Raynaud disease, calciphylaxis, pyoderma gangrenosum). Furthermore, patients with connective tissue disorders that demonstrably affected cutaneous wound healing were excluded from the review. Patients undergoing chemotherapy or radiation therapy at the time of the HAMA application, or who had previously received radiation at the wound site, were also excluded from the review due to the potential of radiation effects on cellular function. Sample selection criteria are displayed in Fig 1.

Statistical analysis

Descriptive statistics included the calculation of PAR, derived from manual wound surface area measurements obtained immediately before each HAMA application and continuing up to 14 days after the final application in the treatment series. All descriptive analyses were conducted using Microsoft Excel (Microsoft Corp., US) and included patient demographics, baseline patient and wound characteristics, mean wound surface area after each HAMA application, and PAR achieved following each application.

Inferential statistical analyses compared the initial wound surface area with the final wound surface area. All inferential tests for the hard-to-heal wounds were performed using IBM SPSS Statistics, version 29.0.2.0 (IBM Corp., US) and Python 3.12, version 0.28 (Python Software Foundation, US). Mean wound areas of the pre- and post-HAMA application series were compared using a paired-samples t-test, with effect size reported as Cohen's d. The strength of the linear relationship between wound size and the number of HAMA applications was evaluated using Pearson's correlation coefficient (r). Lastly, time-to-event analysis was performed to estimate the probability of healing over time. A Kaplan–Meier survival curve was constructed to determine the probability of wound healing (survival probability in days to complete wound closure) for all healed wounds included in the analysis, with healing defined as full re-epithelialisation confirmed at the last HAMA application or within 14 days of follow-up.

A two-tailed α level of 0.05 was adopted and results were considered statistically significant at $p<0.05$; 95% confidence intervals (CIs) were computed for all primary

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comparisons. Prior to analysis, outliers were identified and excluded using the interquartile range (IQR) method. Values were considered extreme outliers if they were <(Q1–1.5×IQR) or >(Q3+1.5×IQR) for PAR or wound area, as appropriate. This non-parametric approach was chosen for its robustness to non-normally distributed data commonly observed in wound healing studies.

Results

Patient and wound characteristics

The study sample comprised 80 patients with a mean age of 73.38±13.52 years. Approximately 79.3% of participants were aged ≥65 years. The most prevalent comorbidities among the cohort were: hypertension (66.25%); hyperlipidaemia (40.0%); and diabetes (42.5%), with a mean haemoglobin A1c (HbA1c) of 6.81±1.39%. The racial distribution was 80.0% White and 20.0% Black. Sex was evenly distributed, with 40 (50.0%) male patients and 40 (50.0%) female patients. Current nicotine use during the treatment period was reported in only 7.5% of patients.

A total of 83 wounds were included in the analysis, comprising 15 DFUs, four VLUs, 17 PIs and 47 (56.6%) open wounds. The majority of wounds (63.9%) were managed in a private outpatient clinic setting. Home-based treatment accounted for 22.9% of cases, while 13.3% were treated in skilled nursing or long-term care facilities. Patient demographics are presented in Table 1, while wound characteristics are shown in Table 2.

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart showing sample selection criteria. CAMP—cellular, acellular and matrix-like product; CTP—cellular and/or tissue-based product; HAMA—hydrated amniotic membrane allograft; LCD—Local Coverage Determination

Sample selection criteria	Patients	Wounds
Patients with hard-to-heal wounds having received a CAMP series between 3 January 2018 and 31 July 2025	1475	1946
↓		
Wounds having completed a HAMA series between 13 November 2024 and 31 July 2025	167	185
↓		
Excluding wounds with >21 days between HAMA applications	163	181
↓		
Excluding those wounds without improvement within the first 4 HAMA applications (per proposed LCD guidelines)	146	159
↓		
Excluding wounds that did not complete a HAMA series (defined as receiving up to 15 applications or healed prior to 15 CTP applications)	84	87
↓		
Excluding patients diagnosed with connective tissue disorders affecting the cutaneous tissue (i.e., pyoderma granulosum)	84	87
↓		
Excluding patients with active cancer, those who are undergoing chemotherapy or radiation therapy, and patients with a history of radiation at the wound site	84	87
↓		
Outliers removed using interquartile range method	80	83

Area reduction

The mean PAR increased progressively with each application of the HAMA series, culminating in a mean PAR of 84.3%. When examined by wound aetiology, open wounds demonstrated the most consistent response, exhibiting a steady reduction in surface area after each HAMA application. In contrast, other wound aetiologies displayed transient fluctuations during treatment. VLUs showed a temporary increase in size of approximately 2cm^2 following the fifth application, before resuming a downward trajectory. DFUs and PIs showed modest increases after the fifth application, with PIs exhibiting a further minor rebound of 0.01cm^2 after the ninth application. Despite these interruptions, all wound types ultimately achieved substantial reductions.

Across the cohort, DFUs had an initial mean area of 6.72±9.29cm^2 and reduced to a mean of 2.24±6.08cm^2, after receiving up to 15 HAMA applications. DFUs had a mean of 9.80±3.26 applications and resulted in a PAR of 84.52%. VLUs, despite the small sample size (n=4), initially had the largest mean area of 14.53±17.02cm^2 and demonstrated the largest PAR of 94.38%, reaching a final mean area of 0.38±0.54cm^2. PIs had an initial mean area of 5.91±4.10cm^2, decreasing to 1.65±3.26cm^2 after a mean of 8.35±3.06 applications, yielding a PAR of 79.47%. Hard-to-heal open wounds (n=47) presented with a mean initial area of 10.32±11.96cm^2, which reduced to 1.92±4.62cm^2 after a mean of 7.78±3.42 applications, yielding a final PAR of 85.07%. The median number of HAMA applications across all wound aetiologies was 10. The mean wound area per application is presented in Table 3, while the mean PAR per application is shown in Table 4.

Healed wound characteristics

A total of 46 (55.42%) wounds achieved complete healing with HAMA. These healed wounds comprised: eight DFUs (53.33% of all DFUs); two VLUs (50.0% of all VLUs); eight PIs (47.06% of all PIs); and 28 open wounds (59.57% of all open wounds). Across all healed hard-to-heal wounds, the mean number of applications required was 6.54±3.22 (median: 6). By wound aetiology, VLUs required the highest mean number of applications (10.00±2.83; median: 10), followed by DFUs (8.38±3.66; median: 8.5), PIs (6.00±2.93; median: 5), and open wounds, which required the fewest applications to achieve complete wound closure (5.93±2.99; median: 5.5).

Overall, the majority of wounds that ultimately healed achieved closure by the sixth HAMA application, after which the cumulative healing rate plateaued. The cumulative healing curve stabilised after the eleventh application. Among the wound aetiologies, hard-to-heal open wounds demonstrated the steepest positive

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Table 1. Patient demographics

	All patients (n=80)	DFU patients (n=15)	VLU patients (n=4)	PI patients (n=15)	OW patients (n=46)
Treatment setting, n (%)					
Private clinic	53 (63.86)	10 (19.61)	3 (5.88)	5 (9.8)	33 (64.71)
Home	19 (22.86)	5 (27.78)	0 (0)	4 (22.22)	9 (50)
Nursing home	11 (13.25)	0 (0)	1 (9.09)	6 (54.55)	4 (36.36)
Age, years, mean±SD	73.38±13.52	69.73±15.99	71.5±13.6	69.2±18.22	76.09±10.38
Age >65 years, n (%)	68 (85)	10 (66.67)	3 (75)	12 (80)	41 (89.13)
Sex, n (%)					
Male	40 (50)	6 (40)	3 (75)	7 (46.67)	24 (52.17)
Female	40 (50)	9 (60)	1 (25)	8 (53.33)	22 (47.83)
Race or ethnicity, n (%)					
Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Black	16 (20)	6 (40)	0 (0)	5 (33.33)	5 (10.87)
Hispanic	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Native American	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
White	64 (80)	9 (60)	4 (100)	10 (66.67)	41 (89.13)
Current nicotine use, n (%)	6 (7.5)	1 (6.67)	1 (25)	2 (13.33)	2 (4.35)
Comorbidities, n (%)					
Diabetes	34 (42.5)	15 (100)	2 (50)	3 (20)	14 (30.43)
HbA1c, mean±SD	6.81±1.39	6.44±1.0	6.35±1.77	6.12±0.39	7.72±1.74
Hypertension	53 (66.25)	9 (60)	4 (100)	6 (40)	34 (73.91)
Hyperlipidaemia	32 (40)	7 (46.67)	3 (75)	5 (33.33)	17 (36.96)
Chronic atrial fibrillation	17 (21.25)	0 (0)	2 (50)	2 (13.33)	13 (28.26)
Congestive heart failure	17 (21.25)	5 (33.33)	2 (50)	1 (6.67)	9 (19.57)
Chronic renal disease	14 (17.5)	4 (26.67)	1 (25)	2 (13.33)	7 (15.22)
Anaemia	11 (13.75)	2 (13.33)	1 (25)	3 (20)	5 (10.87)
Cerebrovascular disease	7 (8.75)	1 (6.67)	4 (100)	4 (26.67)	2 (4.35)
Spinal cord injury	7 (8.75)	1 (6.67)	4 (100)	3 (20)	3 (6.52)
Cancer	9 (11.25)	0 (0)	4 (100)	0 (0)	9 (19.57)

DFU—diabetic foot ulcer; HbA1c—haemoglobin A1c; OW—open wound; PI—pressure injury; SD—standard deviation; VLU—venous leg ulcer

trend in cumulative healing with successive applications. The number of healed wounds per HAMA application is presented in Table 5, while the number of healed wounds within each aetiology is shown in Table 6.

Inferential statistics

A paired samples t-test was conducted to evaluate the change in wound surface area from baseline to the end of treatment with the HAMA across all hard-to-heal wounds (Table 7). The analysis revealed a statistically significant reduction in mean wound areas (t(df)=7.17; p<0.001, where df=degrees of freedom), with a moderate-to-large effect size (Cohen's d=0.79), as shown in Table 8. Subgroup analyses by wound aetiology were also performed using paired samples t-tests. Significant reductions in wound area (p<0.001) were observed for DFUs (t(df)=3.93; p=0.002), PIs (t(df)=7.59; p<0.001) and open wounds (t(df)=5.56; p<0.001). Although VLUs

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Table 2. Wound characteristics

	All wounds (n=83)	DFUs (n=15)	VLUs (n=4)	PIs (n=17)	OWs (n=47)
Treatment setting, n (%)					
Private clinic	53 (63.86)	10 (18.87)	3 (5.66)	6 (11.32)	34 (64.15)
Home	19 (22.89)	5 (26.32)	0 (0.00)	5 (26.32)	9 (47.37)
Nursing home	11 (13.25)	0 (0.00)	1 (9.09)	6 (54.55)	4 (36.36)

Some percentages may not sum to 100 due to rounding. DFU—diabetic foot ulcer; OW—open wound; PI—pressure injury; VLU—venous leg ulcer

Table 3. Average wound area after each Membrane Wrap Hydro application

	All wounds (n=83)	DFUs (n=15)	VLUs (n=4)	PIs (n=17)	OWs (n=47)
Area after application, cm^2, mean±SD					
Initial area	8.97±10.69	6.72±9.27	14.53±17.02	5.91±4.1	10.32±11.96
Application 1	7.07±9.36	5.27±8.32	10.57±12.01	4.14±3.53	8.41±10.69
Application 2	5.69±8.19	4.22±7.16	6.92±5.71	3±3.15	7.03±9.64
Application 3	4.81±7.60	3.45±5.41	6.17±6	2.67±3.61	5.9±9.13
Application 4	3.62±6.48	3.04±5.14	4.39±3.6	1.92±3.08	4.35±7.81
Application 5	3.53±6.34	3.16±5.47	6.47±8.63	2.25±3.79	3.86±7.16
Application 6	2.90±6.12	3.08±6.55	2.95±1.43	1.95±3.44	3.18±7
Application 7	2.61±5.94	2.85±6.36	1.46±0.72	1.79±2.91	2.93±6.86
Application 8	2.41±5.73	2.56±6.08	0.96±0.76	1.98±3.62	2.63±6.51
Application 9	2.09±4.78	2.35±5.92	0.58±0.42	1.99±3.65	2.17±5.01
Application 10	2.08±4.79	2.35±5.93	0.58±0.42	1.96±3.66	2.17±5.02
Application 11	2.06±4.80	2.39±5.94	0.48±0.43	1.92±3.68	2.15±5.03
Application 12	2.06±4.79	2.4±5.93	0.48±0.43	1.92±3.68	2.14±5.03
Application 13	2.04±4.80	2.37±5.94	0.4±0.49	1.92±3.68	2.12±5.04
Application 14	2.04±4.81	2.35±5.95	0.4±0.49	1.92±3.68	2.12±5.04
Application 15	1.85±4.53	2.24±6.08	0.38±0.54	1.65±3.26	1.92±4.62
Applications received, mean±SD, median	8.42±3.31, 10	9.80±3.26, 10	10.00±1.63, 10	8.35±3.06, 10	7.87±3.42, 10

DFU—diabetic foot ulcer; OW—open wound; PI—pressure injury; SD—standard deviation; VLU—venous leg ulcer

demonstrated a numerical decrease in area, the reduction was not statistically significant (t(df)=1.64; p=0.2). Effect sizes were large across all aetiologies, with particularly large effects observed for DFUs (Cohen's d=1.01) and PIs (Cohen's d=1.84).

A Pearson correlation was computed to examine the relationship between the number of HAMA applications and the mean wound area across the entire sample. Throughout the retrospective analysis, varying correlation patterns were observed between the number of HAMA applications and mean wound area without associated statistical significance across aetiologies. The Pearson correlation analysis is displayed in Table 9.

Time to healing was assessed using Kaplan–Meier survival analysis, with 'days to complete wound closure' as the time variable, and censoring applied to wounds that remained unhealed at the end of the observation period. Among wounds that achieved complete healing (n=46), the median time to healing was 42 days (range: 7–110 days). The survival curve exhibited a steady decline, approaching zero probability of remaining unhealed by approximately 100 days, confirming that the majority of wounds that ultimately healed did so within approximately 100 days of treatment initiation. Kaplan–Meier survival analysis is shown in Table 10 and Fig 2.

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Table 4. Percent area reduction (PAR) after each Membrane Wrap Hydro application

	All wounds (n=83)	DFUs (n=15)	VLUs (n=4)	PIs (n=17)	OWs (n=47)
PAR after application, %, mean±SD					
Initial	0±0	0±0	0±0	0±0	0±0
Application 1	26.89±26.11	30.43±22.89	25.38±24.71	33.45±17.11	23.52±29.7
Application 2	43.89±31.47	48.54±27.85	39.48±33.43	52.17±27.66	39.79±33.75
Application 3	55.02±32.09	58.76±27.03	50.77±28.54	61.34±30.24	51.91±34.8
Application 4	65.13±29.48	61.78±28.76	61.49±22.29	72.24±28.42	63.93±30.98
Application 5	65.75±32.61	56.51±32.15	61.48±13.65	69.2±39.23	67.81±31.54
Application 6	71.65±31.64	63.83±27.13	67.62±17.75	72.82±33.67	74.06±33.44
Application 7	74.09±30.63	65.23±33.81	78.56±13.62	74.3±29.44	76.45±31.28
Application 8	77.55±29.65	74.65±26.6	84.36±11.25	72.83±36.36	79.6±29.4
Application 9	80.32±27.63	78.47±24.94	90.41±6.44	73.85±35.68	82.4±26.38
Application 10	79.71±30.2	79.62±23.82	90.41±6.44	74.55±36.08	80.7±31.26
Application 11	80.2±30.39	79.92±24.45	92.41±5.96	75.56±36.42	80.93±31.29
Application 12	80.01±30.42	78.56±24.76	92.41±5.96	75.56±36.42	81.03±31.26
Application 13	80.78±30.55	80.07±24.59	93.84±7.13	75.57±36.42	81.79±31.44
Application 14	81.04±30.62	81.24±25.04	93.84±7.13	75.57±36.42	81.86±31.46
Application 15	84.27±23.94	84.52±25.07	94.38±7.03	79.47±27.3	85.07±23.44
Applications received, mean±SD (median)	8.42±3.31 (10)	9.80±3.26 (10)	10.00±1.63 (10)	8.35±3.06 (10)	7.87±3.42 (10)

DFU—diabetic foot ulcer; OW—open wound; PI—pressure injury; SD—standard deviation; VLU—venous leg ulcer

Discussion

In the present study, a statistically significant and clinically meaningful reduction in mean wound surface area was observed following each treatment series, accompanied by large effect sizes across multiple wound aetiologies. Additionally, Kaplan–Meier analysis demonstrated differences in time to closure (wound survival curve), indicating greater predictability of healing trajectories with continued use of HAMA.

This retrospective analysis describes observed outcomes with HAMA across a broad spectrum of hard-to-heal wound aetiologies, with closure rates and PAR comparable to those reported in previous studies of amniotic products for DFUs and VLUs.[16,17] Observed healing rates were comparable to those previously reported in the literature for CAMP therapies in DFUs and VLUs, suggesting that the therapeutic mechanism of HAMA extends beyond these traditionally studied indications.[16–18] The findings of this retrospective review accord with previous research establishing the efficacy of CAMPs across hard-to-heal wound types in Medicare private practice models.[16] The observed consistent performance across diverse aetiologies is hypothesis-generative and suggests that HAMA may target shared pathophysiological pathways that impair healing in hard-to-heal wounds, irrespective of aetiology. Across the review, complete wound closure was typically achieved after a mean of approximately six applications, underscoring potential reproducibility in real-world clinical settings, though causality cannot be inferred without randomised data.

The management of hard-to-heal wounds is guided by underlying aetiology, yet optimal care universally emphasises the establishment of a clean, infection-free wound bed, typically achieved through meticulous debridement. SoC interventions remain the cornerstone of hard-to-heal wound management. Nevertheless, the present retrospective analysis provides observational evidence of associations supporting the adjunctive use of HAMA with conventional therapies, with observed increases in the probability of complete re-epithelialisation and PAR in hard-to-heal wounds.

Stringent inclusion and exclusion criteria were implemented to maximise internal validity and to isolate the therapeutic contribution of HAMA in the management of hard-to-heal wounds. Patients were systematically excluded if they presented with advanced systemic inflammatory conditions (e.g., severe pyoderma gangrenosum) or were receiving active antineoplastic chemotherapy, as these comorbidities

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Table 5. Healed wound characteristics after application of HAMA

	All wounds (n=83)	DFUs (n=15)	VLUs (n=4)	PIs (n=17)	OWs (n=47)
Healed after application, n (%)					
Application 1	1 (2.17)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.57)
Application 2	3 (6.52)	0 (0.00)	0 (0.00)	0 (0.00)	3 (10.71)
Application 3	9 (19.57)	1 (12.50)	0 (0.00)	1 (12.50)	7 (25.00)
Application 4	12 (26.09)	1 (12.50)	0 (0.00)	3 (37.50)	8 (28.57)
Application 5	21 (45.65)	2 (25.00)	0 (0.00)	5 (62.50)	14 (50.00)
Application 6	26 (56.52)	2 (25.00)	0 (0.00)	6 (75.00)	18 (64.29)
Application 7	31 (67.39)	3 (37.50)	0 (0.00)	6 (75.00)	22 (78.57)
Application 8	34 (73.91)	4 (50.00)	1 (50.00)	6 (75.00)	23 (82.14)
Application 9	36 (78.26)	6 (75.00)	1 (50.00)	6 (75.00)	23 (82.14)
Application 10	39 (84.78)	6 (75.00)	1 (50.00)	7 (87.50)	25 (89.29)
Application 11	43 (93.48)	7 (87.50)	1 (50.00)	8 (100.00)	27 (96.43)
Application 12	44 (95.65)	7 (87.50)	2 (100.00)	8 (100.00)	27 (96.43)
Application 13	45 (97.83)	7 (87.50)	2 (100.00)	8 (100.00)	28 (100.00)
Application 14	45 (97.83)	7 (87.50)	2 (100.00)	8 (100.00)	28 (100.00)
Application 15	46 (100.00)	8 (100.00)	2 (100.00)	8 (100.00)	28 (100.00)
Applications to achieve closure, mean±SD (median)	6.54±3.22 (6)	8.38±3.66 (8.50)	10±2.83 (10)	6.00±2.93 (5)	5.93±2.99 (5.5)

DFU—diabetic foot ulcer; HAMA-hydrated amniotic membrane allografts; OW—open wound; PI—pressure injury; SD—standard deviation; VLU—venous leg ulcer

could confound outcome interpretation and preclude reliable attribution of any wound-healing effects of HAMA intervention. Through these rigorous selection measures, extraneous variables were controlled, strengthening causal inference regarding the efficacy of HAMA and enhancing the overall robustness of the findings. Although it might be posited that patients with the aforementioned systemic conditions are unsuitable candidates for HAMA therapy, there is substantial evidence from studies that demonstrates favourable outcomes, including accelerated healing, with repeated CAMP applications in such cohorts.[19,20] Accordingly, the exclusion criteria used in this present study should not be construed as a contraindication to CAMP use in these complex patients in clinical practice; instead, they reflect a methodological imperative to generate a controlled, generalisable evidence base that can meaningfully inform SoC decision-making for the broader hard-to-heal wound population.

Furthermore, this investigation offers a distinctive examination of HAMA administration within the community-based outpatient setting, an area that remains markedly underrepresented in the existing literature. A salient advantage of this care delivery model is the substantial mitigation of patient-borne transportation burdens and associated costs, which are often prohibitive for individuals requiring frequent clinic visits to tertiary or hospital-affiliated wound centres. Although domiciliary or community-clinic application may introduce constraints on the rigour of serial debridement and wound-bed optimisation—potentially attenuating treatment efficacy compared

Table 6. Healed characteristics for Membrane Wrap Hydro for each aetiology

All wounds		DFUs		VLUs		PIs		OWs	
Total, n	Healed, n (%)	Total, n (%)	Healed, n (%)	Total, n (%)	Healed, n (%)	Total, n (%)	Healed, n (%)	Total, n (%)	Healed, n (%)
83	46 (55.42)	15 (18.07)	8 (53.33)	4 (4.82)	2 (50)	17 (20.48)	8 (47.06)	47 (56.63)	28 (59.57)

Percentages displayed are the healed percentage of the individual aetiology type. DFU—diabetic foot ulcer; OW—open wound; PI—pressure injury; VLU—venous leg ulcer

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Table 7. Results of the paired samples t-test comparing initial wound areas and after the last Membrane Wrap Hydro application

	Paired differences					t	df	p-value	
	M	SD	SEM	95% CI of the difference				1-sided	2-sided
				Lower	Upper				
All	7.12	9.05	0.99	5.15	9.10	7.17	82	<0.001	<0.001
DFUs	4.48	4.42	1.14	2.03	6.92	3.93	14	<0.001	0.002
VLUs	14.15	17.25	8.63	-13.31	41.6	1.64	3	0.1	0.2
PIs	4.26	2.31	0.56	3.07	5.45	7.59	16	<0.001	<0.001
OWs	8.41	10.36	1.51	5.36	11.45	5.56	46	<0.001	<0.001

CI—confidence interval; df—degrees of freedom; DFU—diabetic foot ulcer; M—mean; OW—open wound; PI—pressure injury; SD—standard deviation; VLU—venous leg ulcer; SEM—standard error of the mean

Table 8. Cohen's d effect size of means

	Standardiser	Point estimate	95% CI	
			Lower	Upper
All	9.05	0.79	0.54	1.03
DFUs	4.42	1.01	0.37	1.63
VLUs	17.25	0.82	-0.39	1.94
PIs	2.31	1.84	1.04	2.62
OWs	10.36	0.81	0.48	1.14

DFU—diabetic foot ulcer; OW—open wound; PI—pressure injury; VLU—venous leg ulcer

with specialised inpatient or advanced outpatient facilities—this approach concomitantly enhances equitable access to advanced biologic therapies. By diminishing geographical and logistical barriers, community-based HAMA administration extends evidence-based wound care to traditionally underserved populations, thereby broadening the sociodemographic spectrum of patients who can benefit from these interventions and promoting greater inclusivity in hard-to-heal wound management.

A growing body of evidence substantiates the efficacy of amniotic cellular-based products in achieving clinically meaningful reductions in hard-to-heal wound dimensions.[17,21,22] The present investigation uniquely contributes by quantifying the incremental change in wound surface area attributable to each successive HAMA application throughout a 15-week treatment course, encompassing hard-to-heal wounds of diverse aetiologies. Serial measurements revealed consistent mean reductions in all hard-to-heal wound areas with each application, underscoring a dose–response relationship.

Notably, the magnitude of therapeutic response observed for hard-to-heal PIs and open wounds was comparable to, and in certain subgroups marginally superior to, that documented for the more extensively studied DFUs and VLUs. Mean PAR per application, as well as the proportion of wounds achieving complete closure milestones, aligned closely or exceeded benchmark outcomes previously reported for DFUs and VLUs in both RCTs and real-world registries.[18,23]

These findings challenge the prevailing wisdom that has historically prioritised DFUs and VLUs in regulatory approvals and coverage determinations, while often marginalising PIs and dehisced surgical or traumatic open wounds. Whereas optimal CAMP application frequency has been relatively well delineated for DFUs and VLUs, corresponding data for other aetiologies remains sparse. The current results provide preliminary, observational evidence of a dose–response relationship across wound aetiologies. These findings are hypothesis-generative and suggest the potential for broader application, though confirmatory controlled studies are needed to evaluate efficacy relative to SoC. This body of real-world evidence demonstrates associations indicating that HAMA represents a mature, reproducible and broadly effective therapeutic modality for hard-to-heal wound management across diverse clinical presentations.

A formal health-economic evaluation—incorporating both direct and indirect costs—is imperative to quantify the incremental cost-effectiveness of specific HAMA treatment across hard-to-heal wound aetiologies. The comparable clinical efficacy demonstrated herein for PIs and open wounds relative to DFUs and VLUs raises the prospect of aetiology-agnostic treatment algorithms that could streamline clinical decision-making and reduce practice variation. However, reimbursement and adoption barriers are frequently governed by payer-specific cost-effectiveness thresholds; thus, aetiology-stratified pharmacoeconomics modelling is particularly needed for PIs and open wounds, where existing analyses remain sparse. Addressing these economic dimensions, alongside long-term outcomes, such as recurrence rates and quality-adjusted life-years, will be essential to overcome implementation barriers and to facilitate equitable integration of effective HAMA into evidence-based wound care pathways.

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Table 9. Pearson correlation coefficients between the number of applications and wound area after each Membrane Wrap Hydro application

		App 1	App 2	App 3	App 4	App 5	App 6	App 7	App 8	App 9	App 10	App 11	App 12	App 13	App 14	App 15
All	Pearson correlation	0.169	0.202	0.235	0.276	0.278	0.265	0.254	0.236	0.239	0.237	0.231	0.232	0.225	0.223	0.218
	Sig (2-tailed)	0.128	0.067	0.033	0.011	0.011	0.016	0.020	0.031	0.030	0.031	0.036	0.035	0.041	0.043	0.048
	n	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83
DFUs	Pearson correlation	0.077	0.101	0.121	0.136	0.130	0.100	0.105	0.085	0.081	0.076	0.076	0.082	0.076	0.070	0.050
	Sig (2-tailed)	0.785	0.720	0.667	0.628	0.643	0.724	0.709	0.763	0.775	0.788	0.786	0.772	0.789	0.804	0.859
	n	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
VLUs	Pearson correlation	-0.778	-0.702	-0.707	-0.693	-0.798	-0.966	0.285	0.713	0.697	0.697	0.287	0.287	0.000	0.000	0.000
	Sig (2-tailed)	0.222	0.298	0.293	0.307	0.202	0.034	0.715	0.287	0.303	0.303	0.713	0.713	1.000	1.000	1.000
	n	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
PIs	Pearson correlation	0.048	0.259	0.337	0.379	0.357	0.352	0.392	0.332	0.329	0.318	0.304	0.304	0.304	0.304	0.299
	Sig (2-tailed)	0.854	0.315	0.185	0.133	0.160	0.165	0.120	0.194	0.197	0.213	0.236	0.236	0.236	0.236	0.244
	n	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
OWs	Pearson correlation	0.287	0.297	0.320	0.352	0.363	0.326	0.308	0.287	0.296	0.297	0.291	0.290	0.281	0.280	0.288
	Sig (2-tailed)	0.050	0.043	0.028	0.015	0.012	0.025	0.035	0.051	0.043	0.043	0.048	0.048	0.056	0.056	0.050
	n	47	47	47	47	47	47	47	47	47	47	47	47	47	47	47

App—application; DFU—diabetic foot ulcer; OW—open wound; PI—pressure injury; Sig—significance; VLU—venous leg ulcer

Limitations

The present retrospective analysis is subject to several methodological limitations that warrant consideration when interpreting the findings. The modest sample size constrained statistical power and limited the precision of effect size estimates, particularly in subgroup analyses stratified by wound aetiology—and may have contributed to the unsuccessful Pearson correlation analysis (insufficient observations at later application timepoints after wounds progressively healed or were censored). A larger cohort would strengthen the robustness of the observed outcomes and facilitate more granular exploration of potential modifiers of treatment responses.

Data were extracted primarily through automated EHR queries, with subsequent manual chart adjudication to verify accuracy and completeness. Although this hybrid approach mitigated errors inherent in fully automated retrieval, the analysis remained dependent on the fidelity of diagnostic and procedural coding practices. Inaccuracies or inconsistencies in coding could have introduced misclassification bias, potentially affecting patient inclusion and outcome attribution.

Restricted access to data from hospital outpatient departments (HOPDs)—the predominant setting in which advanced hard-to-heal wound care is delivered—precluded a comprehensive, real-world evaluation across the full continuum of care environments. Although this analysis encompassed primarily private practice clinics, mobile wound care and nursing home settings, the limited HOPD settings introduced a risk of selection bias, as community-based clinics may systematically differ from HOPDs in patient demographics, wound complexity, provider expertise and adherence to evidence-based protocols. Consequently, the study cohort was disproportionately

Table 10. Results of the Kaplan–Meier survival curve to determine the probability of days to healed wounds

Mean*				Median			
		95% confidence interval				95% confidence interval	
Estimate	Standard error	Lower bound	Upper bound	Estimate	Standard error	Lower bound	Upper bound
46.609	3.392	39.961	53.256	42.000	2.802	36.508	47.492

*Estimation is limited to the largest survival time if it is censored

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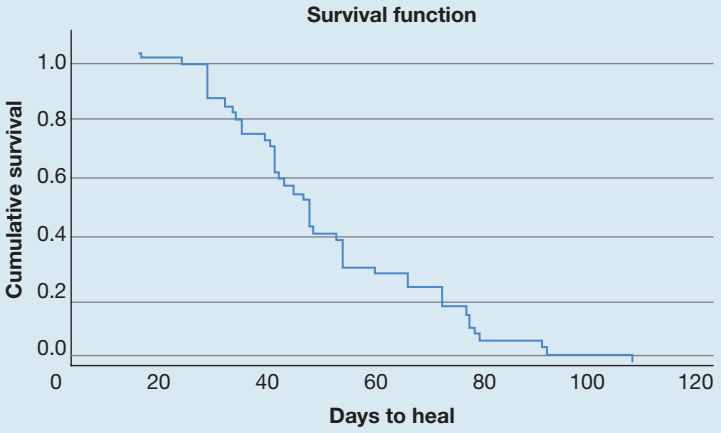
Fig 2. Results of the Kaplan–Meier survival curve to determine the probability of days to healed wounds



composed of patients aged >65 years, which may have compromised the external validity and generalisability of the results to younger populations. Future investigations should prioritise multisite designs that incorporate HOPD and non-HOPD settings and include patients across a broad range of payer types. Such efforts will be essential for generating high-quality, representative evidence to inform clinical practice and reimbursement policy for the diverse population affected by hard-to-heal wounds.

Further, the present analysis did not stratify outcomes by wound depth or the presence of exposed critical structures (e.g., bone, tendon, joint capsules or hardware). Deep hard-to-heal wounds with osteomyelitis, tendinous involvement, or biofilm-colonised foreign material represent a distinct therapeutic challenge and may exhibit attenuated responses to skin substitutes that primarily target dermal regeneration. Dedicated studies examining the efficacy of HAMA in stage IV PIs, exposed-tendon DFUs, and postoperative dehiscence with underlying structural exposure are therefore warranted to delineate the boundaries of current HAMA utility and to guide rational escalation to reconstructive or regenerative alternatives.

A fundamental limitation of the present investigation was the absence of a concurrent control cohort managed exclusively with SoC interventions without use of HAMA. Without a parallel non-HAMA arm, the observed wound area reductions cannot be definitively disentangled from the intrinsic (albeit typically protracted) healing trajectory of hard-to-heal wounds under optimised conventional therapy. The natural healing process of untreated or SoC-managed hard-to-heal wounds of varied aetiologies remains inadequately characterised in contemporary, real-world datasets, underscoring the need for large-scale, prospective registries that systematically document spontaneous healing rates and temporal wound dynamics in the absence of advanced biologics.

This retrospective design is susceptible to unmeasured confounders that may influence observed outcomes. Potential confounders include variations in patient adherence to offloading and compression regimens, subtle differences in nutritional status or glycaemic control not fully captured in chart reviews, frequency and thoroughness of debridement between applications, and provider-specific variations in wound assessment or dressing selection. Furthermore, although rigorous inclusion criteria were applied, residual confounding from unreported comorbidities (e.g., subclinical vascular impairment or low-grade biofilm) or lifestyle factors (e.g., unreported physical activity levels) cannot be ruled out. These factors could have contributed to the observed wound improvements independently of or synergistically with HAMA applications, limiting attribution of outcomes solely to HAMAs.

Although the primary objective of this retrospective analysis was to characterise the per-application therapeutic yield of HAMA rather than to establish superiority over SoC, the inclusion of a rigorously matched control group would substantially strengthen causal inference in future work. Consequently, the reported outcomes—while clinically encouraging—must be interpreted as preliminary, feasibility-level evidence only. The inclusion of a rigorously matched control group would be required to strengthen causal inference and elevate these findings from observational to confirmatory evidence.

Conclusion

Hard-to-heal wounds represent a formidable global healthcare burden, exacting substantial morbidity, diminishing quality of life, and elevating mortality while imposing considerable economic strain on healthcare systems. This retrospective analysis reports observed closure rates and PAR with HAMA in hard-to-heal PIs and open wounds that appear commensurate with outcomes previously reported for DFUs and VLUs in the literature. These findings are observational and hypothesis-generative. They challenge aetiology-specific restrictions frequently embedded in current coverage policies and provide preliminary evidence to guide recommendations and underrepresented hard-to-heal wound aetiologies.

When integrated with optimised SoC, HAMA was associated with favourable outcomes across diverse aetiologies in this observational cohort, suggesting its potential role as a versatile adjunctive therapy. To fully realise this potential, future research must prioritise the identification and validation of patient- and wound-specific predictors of response, thereby enabling precision-guided CAMP deployment. Appropriately powered, multicentre RCTs focused on hard-to-heal PIs and open wounds are now essential to confirm these observational data, delineate optimal treatment algorithms, and generate the high-level evidence required to broaden clinical adoption and equitable reimbursement across the entire spectrum of hard-to-heal wound pathology. **JWC**

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Reflective questions

- How do the observed closure rates and percentage area reductions for pressure injuries and open wounds in this study compare to those typically reported for diabetic foot ulcers and venous leg ulcers in existing literature, and what implications might this have for expanding reimbursement policies for human amniotic membrane allografts (HAMA) across diverse wound aetiologies?
- Considering the retrospective design and limitations, such as the modest sample size and lack of a concurrent control group, what additional methodological enhancements could strengthen causal inferences about the efficacy of HAMA in real-world private practice settings?
- How might patient-specific factors, such as comorbidities or wound depth, influence the optimal number of applications needed to achieve complete closure, and what future research could explore these predictors?

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