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A retrospective matched-cohort study of 3994 lower extremity wounds of multiple etiologies across 644 institutions comparing a bioactive human skin allograft, TheraSkin, plus standard of care, to standard of care alone

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Abstract

Most chronic wounds are related to comorbidities, for which no clinical trials are performed. This retrospective propensity matched-cohort study examined data from 2 074 000 lower extremity wounds across 644 institutions to determine the effectiveness of TheraSkin plus standard of care (SOC; n = 1997) versus SOC alone (n = 1997). Multivariate modelling comparing outcomes such as healing rates, percent area reductions (PARs), amputations, recidivism, treatment completion, and medical transfers were evaluated. A higher proportion of wounds in the treatment group compared with the controls were more likely to close (68.3% versus 60.3%), particularly wounds with exposed structures (64% versus 50.4%) and with lower recidivism at 6 months (24.9% versus 28.3%). The control group was 2.75x more likely to require amputation than the treatment group. The combination of propensity matching and logistic regression analysis on a particularly large database demonstrated that wounds treated with TheraSkin had higher healing rates, higher PARs (78.7% versus 68.9%), fewer amputations, lower recidivism, higher treatment completion (61.0% versus 50.6%), and lower medical transfers (16.1% versus 23.5%) than SOC alone. This study considered data from complex wounds typically excluded from controlled trials and supports the idea that real-world evidence studies can be valid and reliable.

KEYWORDS

allograft, amputation, healing, recidivism, wounds

Abbreviations: BMI, body mass index; BSA, bioactive human skin allograft; CPH, Cox Proportional Hazard; CTP, cellular and/or tissue-based product; DFU, diabetic foot ulcer; EMR, electronic medical record; HCT/P, human cells, tissues, and cellular and tissue-based product; HBOT, hyperbaric oxygen therapy; LCD, local coverage determination; MITT, modified intent-to-treat; NPWT, negative pressure wound therapy; PAR, percent area reduction; RCT, randomised controlled trial; SD, standard deviation; US, United States; VLU, venous leg ulcer.

1 | INTRODUCTION

Non-healing wounds are not so much a disease as a symptom of underlying comorbidities, such as diabetes, venous disease, immunosuppression because of steroid use, renal impairment, autoimmune diseases, dermatologic diseases, or age-related debility or paralysis. Randomised clinical trials (RCTs) for cellular and/or tissue-based products (CTPs) have been mainly restricted to diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) where these comorbidities are either limited or completely excluded. However, Medicare claims data have shown that most chronic wounds among Medicare beneficiaries are chronic ulcers relating to other underlying comorbid diseases for which no clinical trials are performed.[1] Additionally, primary reliance on RCTs poses an inherent challenge for real-world patients: 81.3% of all trials exclude common comorbidities.[2] Unfortunately, comorbid diseases are the underlying cause of many chronic wounds. Because of the strict exclusion criteria, the generalisability of trials investigating chronic wounds is limited, resulting in wound care RCTs only enrolling approximately 4% of the real-world patient population.[3,4] Real-world data obtained from wound-care-specific Electronic Medical Records (EMR) confirm the non-generalisable nature of prospective trials and indicate how considerably larger trial enrolment could be if a more representative population of patients were included.[3,4]

Numerous CTPs are used to stimulate the healing process in patients with chronic wounds.[5,6] These biologically active products can be human, xenograft, and/or synthetic, and they are generally limited to the study and treatment of VLUs and DFUs that do not have any exposed deep structures. Consequently, little clinical data exist to support the use of CTPs in the treatment of other wounds. TheraSkin (Solsys Medical; Newport News, Virginia) is a bioactive human skin allograft (BSA) that is procured from organ donors while the tissue is viable; the skin is minimally manipulated and proprietarily processed for safety.[7-11] BSA is indicated for homologous use (ie, human skin to replace human skin) and, as such, appropriate for all wound types and depths if adequate wound bed preparation and vascularity is present. BSA is regulated by the US Food and Drug Administration as a human cells, tissues, and cellular and tissue-based product under 21CFR Parts 1270 and 1271. The science and use of human skin allografts dates to the early 20th century, and they are still the most globally used skin replacement for wound defects because of burns, trauma, surgery, and chronic non-healing wounds.[12-17] BSA is comparable to fresh human skin and contains living cells, growth factors, and a native human extracellular matrix.[7] In both RCT and real-world studies, BSA has been shown to improve healing in VLUs and DFUs, with and without exposed deep structures.[8-11]

The objective of this large, retrospective, matched-cohort study was not only to determine if there was any benefit to treating lower extremity wounds of a variety of etiologies with BSA plus standard of care (SOC) when compared with SOC alone, but to explore its effectiveness through a real-world study of the actual wound-care population as representative of the true medical challenges of treating and healing chronic wounds. Clinical trials in wound care are severely impacted by typical enrolment criteria, which limits study participation. Furthermore, the results are tempered through the selection of healthier patients with smaller, shallower wounds. Without being bound by stringent clinical trial exclusionary criteria, our study design used propensity matching to create identical cohorts to analyse differences in healing rates, volume-reduction rates, amputations, and wound recidivism as well as treatment completion and medical transfers in wounds that are more commonly seen in the clinical setting.

Key Messages

- most controlled trials studying cellular and/or tissue-based products are limited to venous and diabetic wounds that are small in size and without exposed structures.
- the aim of this study was to demonstrate the effectiveness of TheraSkin plus standard of care (SOC) treatment in a real-world population of wounds below the knee of all etiologies and depths versus SOC alone.
- etiologies included diabetic, pressure, radiation, surgical, trauma, venous, and arterial wounds with and without exposed structures.
- propensity matching and logistic regression analysis were used to create near-identically matched cohorts from a pool of 2 074 000patients across 644 institutions.
- patients treated with TheraSkin (n = 1997) had significantly improved healing outcomes, lower amputation rates, reduced recidivism, and improved patient-centered outcomes than SOC alone (n = 1997) particularly in more complex wounds involving deep structures.

2 | MATERIALS AND METHODS

2.1 | Study design and population

Data were collected from EMRs of patients visiting 644 outpatient wound care centers managed by a large wound management company (Healogics, Jacksonville, Florida) between January 1, 2012 and October 25, 2018. The same company-proprietary and standardised EMR was used at all participating institutions, ensuring reporting consistency.

The company requires all clinicians practicing in the wound-care centers to undergo training and to follow an evidence-based 9-step diagnostic approach; the centers also follow a team-based case management approach that includes evidence-based clinical practice guidelines to follow through the course of treatment. Adherence to the guidelines and reporting are tracked on a monthly basis; in total, the study centers treat over 300 000 wounds annually and as much as 40% of the wounds treated in the outpatient hospital department.

This study adhered to the 1975 Declaration of Helsinki. The Quorum Review Institutional Review Board (now Advarra; Columbia, Maryland) approved this study and determined that the retrospective analysis of Health Insurance Portability and Accountability Act (HIPAA) de-identified International Classification of Diseases (ICD) data was exempt from patient consent requirements. Data were extracted from an initial pool of 2 074 000 lower extremity wounds located below the knee. Wounds were selected that had been treated with either BSA plus SOC (treatment cohort) or SOC alone (control cohort). After excluding ineligible patients and those with significant missing data (ie, wound characteristics) and/or lack of treatment documentation, we were left with data from 833 708 wounds (831 711 wounds treated with SOC and 1997 wounds treated with BSA) (Figure 1). A small number of patients had more than one wound, but only wounds that met the study criteria were included.

Providers at study centers used a case management model that adheres to SOC in order to reduce practice variability through clinical practice guidelines. These clinical practice guidelines define SOC to include optimisation of tissue perfusion and oxygenation, removal of non-viable tissue, resolve infection/inflammation, resolve edema, optimise wound bed moisture balance, enhance tissue growth, and control and diminish pain and optimisation of host factors for all wounds treated at the centers. For the purpose of this research, SOC can be simply defined as medical management (per company's algorithms), debridement, offloading, compression, and moist wound care using any type of non-biological wound dressings. In the BSA cohort, subjects received the product at the physician's discretion, and application was performed in accordance with the manufacturer's recommendations for preparation.

2.2 | Propensity score matching to generate control cohort

We used propensity-matched cohorts to ensure that the treatment and control cohorts were nearly identically matched in characteristics. From the available sample of 831 711 wounds treated with SOC, we identified 1997 wounds from patients that matched the BSA sample of

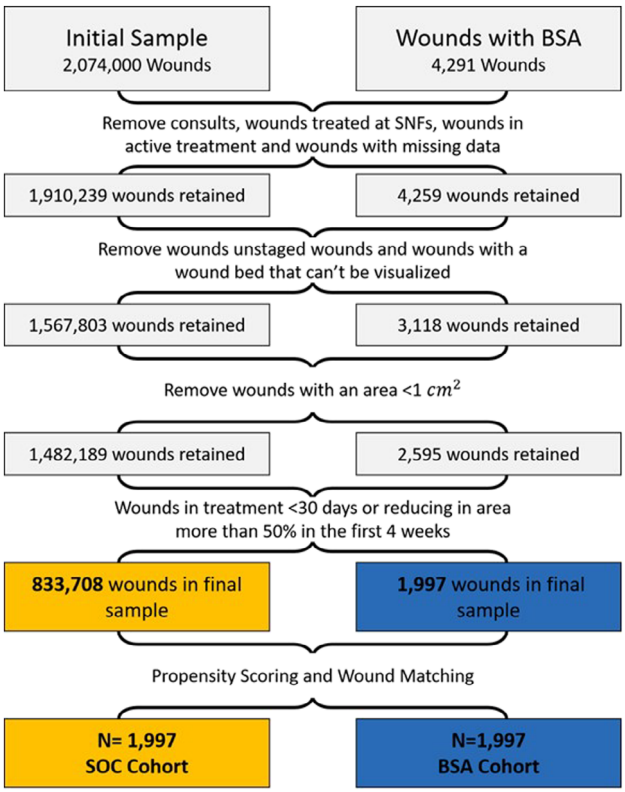

FIGURE 1 Cohort matching. BSA, bioactive human skin allograft

1997 wounds. Descriptive analysis was performed on the unmatched data set in order to identify variables that influence wound healing and have differences between the control and BSA populations.

The patients selected in the control cohort were selected using propensity score matching for each etiology on eight variables related to the wounds that were readily available and reliably reported:

- Wound area (cm^2)
- Wound depth (mm)
- Wound duration [the number of days that the wound was present prior to initiation of treatment in the study (<90, 90 to 179, and 180 days to 1 year)]; for the BSA cohort, the time was measured up until initial treatment with BSA; in the control cohort, the time was measured up until initiation of SOC at one of the study centers
- Wound grade [using the Wagner classification[18]] and stage [using the National Pressure Ulcer Advisory Panel staging[19]]
- Whether the patient was palliative
- Number of complicating comorbidities
- Body Mass Index (BMI)

The following comorbidities and complications were included: Alzheimer's disease, coronary artery disease, cellulitis,

TABLE 1 Patient and wound characteristics, by matched cohort

Variable	BSA n = 1997	Control n = 1997	*P* value
Mean (SD) wound area at first assessment, cm^2	16.2 (25.6)	16.3 (22.4)	.90
Mean (SD) wound depth at first assessment, mm	3.0 (5.0)	3.0 (3.7)	.83
Mean (SD) wound duration at first assessment, days	145 (435.6)	162.7 (430.3)	.18
Mean (SD) patient age, years	67.6 (14.8)	66.1 (14.9)	<.01
Wound severity, n (%)			
Wagner Grade 1	268 (13.4%)	266 (13.3%)	.91
Wagner Grade 2	403 (20.2%)	394 (19.7%)	.70
Wagner Grade 3	123 (6.2%)	132 (6.6%)	.56
Wagner Grade 4	32 (1.6%)	36 (1.8%)	.63
Stage I	5 (0.2%)	8 (0.4%)	.28
Stage II	40 (2.0%)	34 (1.7%)	.48
Stage III	60 (3.0%)	65 (3.3%)	.65
Stage IV	22 (1.1%)	29 (1.5%)	.32
Partial thickness	116 (5.8%)	130 (6.5%)	.35
Full thickness	26 (1.3%)	22 (1.1%)	.56
Full thickness without exposed structures	741 (37.1%)	735 (36.8%)	.85
Full thickness with exposed structures	118 (5.9%)	104 (5.2%)	.34
Other	43 (2.2%)	42 (2.1%)	.72
Palliative patient, n (%)	44 (2.2%)	52 (2.6%)	.41
Diabetic, n (%)	1144 (57.3%)	1094 (54.8%)	.11
Mean (SD) number of comorbidities	0.7 (0.9)	0.7 (0.9)	.75
Mean (SD) Body Mass Index	34.4 (11.2)	32.4 (9.7)	<.0001
Aetiology, n (%)			
Diabetic	828 (41.5%)	831 (41.6%)	.92
Lymphoedema	12 (0.6%)	7 (0.4%)	.25
Pressure injury	166 (8.3%)	171 (8.6%)	.77
Radiation	19 (1%)	17 (0.8%)	.74
Surgical wound	175 (8.8%)	191 (9.56%)	.38
Trauma	149 (7.5%)	149 (7.5%)	1.00
Venous ulcer	575 (28.8%)	583 (29.2%)	.78
Arterial ulcer	73 (3.7%)	48 (2.4%)	.020

Abbreviation: BSA, bioactive human skin allograft plus SOC Control: SOC alone.

chronic obstructive pulmonary disease, congestive heart failure, end-stage renal disease, immunosuppressive conditions, morbid obesity, peripheral vascular disease (arterial and venous), smoking status, and venous insufficiency. The incidence of diabetes was also considered and found to be identical between the two cohorts (Table 1).

The Matchit package version 3.0.2 in R (R Foundation, 2018) was used to created propensity-matched cohorts. The propensity was constructed on a logit-linked generalised linear model, and the nearest neighbour method was then used to match subjects. Sufficient fit was measured by the overall mean distance reduction.

Across the eight variables, the non-matched data had a mean difference in distance of 0.0012, with a maximum empirical quantile function distance of 0.2157. After applying propensity matching, the matched pairs had a mean difference in distance of <0.0001, with a maximum eQQ distance of 0.0001. The matched cohorts were nearly identical, with the exception that the BSA cohort had a higher age and mean BMI than the control cohort (Table 1).

2.3 | Patient enrolment starting points

All potential subjects were given a 4-week window of observation during which they received SOC prior to their enrolment. Potential subjects who were in active treatment or demonstrated 50% or more closure of their wounds during this time period were excluded from the analysis. Time to heal was measured from the completion of the 4-week observation period for the control cohort and from the first date of BSA application for the BSA cohort. The modified intent-to-treat (MITT) population included all wounds in both groups that were enrolled after the 4-week observation period. The completed treatment population included all wounds that completed the study.

2.4 | Healing rates

Healing was defined as full epithelialisation of the wounds with no open areas. Among the MITT population, we also analysed the mean percent area reduction (PAR) of the wounds. Mean PAR was based on an assessment of all wounds included in this study, except those that grew to more than four times the original size over the course of treatment. Numerous healing factors were analysed, including the percentage of total wound closure, wound duration prior to enrolment, and initial wound depth (partial/full thickness and the presence of exposed structure). Wounds with exposed structures were analysed both collectively and individually among the cohorts. The closure rate was also examined based on wound location (toe, foot, or lower leg).

Wounds were further analysed in each cohort according to the wound duration prior to initial treatment, aetiology, percentage closed, and amputation rates (based on all amputations from partial toe to below the knee) within the first 20 weeks after treatment initiation, PAR, and recidivism rates at 3, 6, and 12 months. Patient-discharge outcomes, including the disposition of the patients after 20 weeks of treatment, treatment completion rates, medical transfer rates (ie, from outpatient wound center to acute care hospital or skilled nursing facility), and expiration rates, were also analysed. The mean number of grafts used in the BSA cohort was examined for each etiology.

Outcomes were separately analysed for wounds with exposed deep structures (muscle, tendon, fascia, joint capsule, or bone), which included Wagner Grade 2-4 diabetic wounds, Stage 4 pressure injuries, and wounds of other etiologies classified as having exposed deep structures. For this subgroup of wounds, overall healing rates, amputation rates, and recidivism rates were analysed for both cohorts.

2.5 | Additional statistical analysis

Frequencies of patient, wound, and outcome measures were measured with descriptive statistics. For continuous measures, the mean and SD were calculated. Healing rates, amputation rates, recidivism rates, and patient-discharge outcomes were compared across cohorts using logistic regression analysis.

Cox Proportional Hazard (CPH) models were created to measure the effect of BSA plus SOC versus SOC alone on the time to heal. The survival package in R was used to fit the CPH Models using the propensity-matched datasets. Kaplan-Meier curves were generated using initial models created with no covariates. Subsequent models were created with the following covariates and their 2-way interactions:

- Etiology
- Wound stage
- Wound area at initial assessment
  - Grouped as small (<5 cm^2), average (5-40 cm^2), large (> 40 cm^2)
- PAR at 4 weeks
  - Grouped as significantly decreasing (>2.5% area reduction), stagnant (± 2.5% area from the initial assessment), and significantly increasing (>2.5% increase in area).

For each etiology, final models were created that retained only significant variables. Their fit was analysed using^2 and model concordance between predicted and actual values, as well as the likelihood ratio, Wald, and Score tests. Model coefficients were analysed. Variables that significantly affected the time to heal were analysed. A dataset comprising predictions for each member of the Cartesian product of the regressors was developed and used to create Kaplan-Meier curves for all possible scenarios.

3 | RESULTS

3.1 | Overall healing rates and PAR

Propensity score matching produced well-matched cohorts for lower-extremity wounds of all etiologies (Table 1). Among both cohorts, there were directionally positive results. Overall, wounds treated with BSA plus SOC were significantly more likely to heal versus SOC alone the controls ($P < .0001$). In the BSA cohort, 68.3% of the wounds closed, while 60.3% closed in the control cohort (Table 3). On average, 2.71 BSA grafts were required to close the healed wounds in the BSA cohort.

Differences in PAR were noted among the two cohorts. The mean PAR for wounds in the BSA cohort was 78.73% (n = 1926) as compared with a mean PAR of 68.85% (n = 1905) for the control cohort. This increase in PAR for the BSA group is statistically significant ($P < .001$) (Table 3).

TABLE 2 Mean number of BSA grafts required to achieve closure, based on wound etiology

Wound type	No. of wounds treated	Mean no. of BSA grafts for wound closure (SD)
Diabetic	559	2.8 (2.2)
Pressure injury	110	2.8 (2.2)
Radiation	13	2.6 (2.2)
Surgical wound	126	2.9 (2.3)
Trauma	122	2.2 (1.4)
Venous ulcer	381	2.6 (1.9)
Arterial ulcer	44	3.2 (1.9)
Lymphoedema	7	2.3 (1.6)

Note: Number of applications to closure is only applicable for wounds which healed over the course of treatment.
Abbreviation: BSA, bioactive human skin allograft.

3.2 | Healing rates by wound duration

Wound duration affected the MITT healing rates (Figure 2). There was a statistically significant difference in the healing rate, in favour of the BSA cohort when compared with the control cohort among wounds with duration of <90 days ($P < .0001$), 90 to 179 days ($P = .0195$), and 180 days to 1 year ($P < .0001$) (Figure 2).

3.3 | Healing rates by wound aetiology

Wound etiology also impacted the healing rate. Among the MITT population, most wounds closed more quickly with BSA plus SOC when compared with SOC alone, but the difference was statistically significant in favour of BSA for arterial wounds ($P = .0325$), diabetic ulcers ($P < .0001$), pressure injuries ($P < .0001$), radiation wounds ($P = .05$), and trauma wounds ($P = .0311$) (Figure 3).

Based on the wound etiology in the BSA cohort, we found slight variations in the number of grafts required to achieve wound closure. A detailed breakdown of the number of grafts required, based on wound etiology, is shown in Table 2.

3.4 | Patient discharge outcomes

The wounds treated with BSA plus SOC had significantly higher completion rates, paired with lower rates of medical transfer to higher acuity of care and fewer patients quitting treatment ($P = .0001$, .0001, and .0027, respectively), as compared with wounds treated with SOC alone. The patient mortality rate was not significantly different between the two cohorts (4.6% versus 5.4%; $P = .25$) (Table 3).

TABLE 3 Healing rates, PAR, recidivism, and disposition outcomes

	BSA	Control	*P* value
Overall healing rate	68.3%	60.3%	$P < .0001$
Percent area reduction (PAR)	60.0%	54.4%	$P < .0001$
Recidivism at 3 months	22.5%	24.7%	$P = .1315$
Recidivism at 6 months	24.9%	28.3%	$P = .0296$
Recidivism at 12 months	32.6%	34.4%	$P = .2964$
Completed treatment	60.99%	50.63%	$P = .0001$
Medical transfer	16.12%	23.54%	$P = .0001$
Quit treatment	17.48%	21.23%	$P = .0027$
Death	4.6%	5.4%	$P = .25$

Abbreviation: BSA, bioactive human skill allograft.

3.5 | Recidivism

There were 1553 wounds with recidivism data available in the control cohort and 1660 in the BSA cohort. At 3 months, the recurrence rate was 22.5% in the BSA cohort versus 24.7% in the control cohort ($P = .1315$). At 6 months, the rate increased to 24.9% in the BSA cohort versus 28.3% in the control cohort, which was a significant difference among cohorts ($P = .0296$). At 12 months, the recidivism rate in the BSA and control cohorts was 32.6% and 34.4%, respectively ($P = .2964$) (Table 3).

3.6 | Amputation rates following treatment

Wounds in the control cohort had 2.75 times more amputations than wounds in the BSA cohort ($P < .0001$), with an amputation rate of only 0.5% in the BSA cohort (n = 1997) versus 1.9% in the control cohort (n = 1997) (data not shown).

3.7 | Wounds with exposed deep structures

There were 698 wounds (35%) in the BSA cohort and 695 wounds (34.8%) in the control cohort that initially had exposed deep structures (Table 1). In the BSA cohort, 64% of these wounds healed, as compared with 50.4% in the control cohort ($P < .0001$). Among wounds that initially had exposed structure, the amputation rate was significantly lower in the BSA cohort with 1.4% fewer wounds resulting in amputation ($P = .0014$) (data not shown).

3.8 | Additional Statistical Analysis

The logistic regression measuring the probability of a wound healing over the course of treatment sufficiently fit the data based on a Hosmer-Lemeshow test ($P = .2658$). The presence of BSA over the course of treatment increases the odds

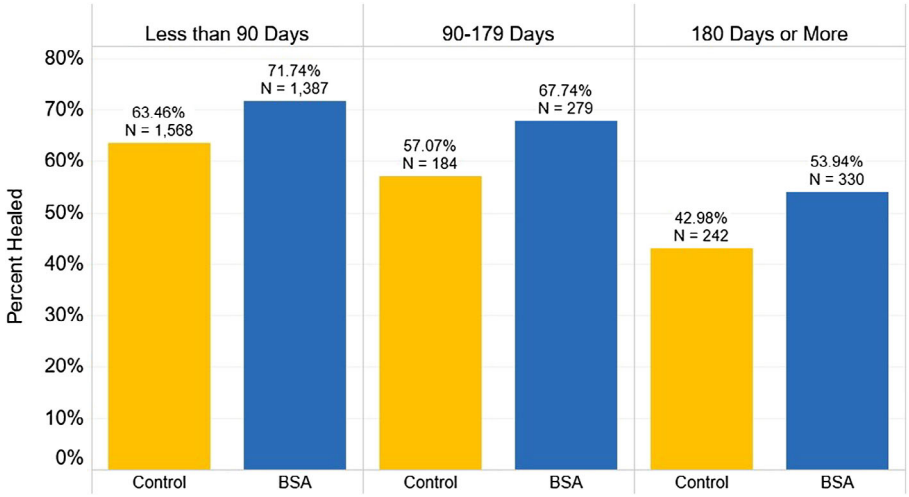

FIGURE 2 Modified intent-to-treat healing rates for wounds based on duration prior to treatment

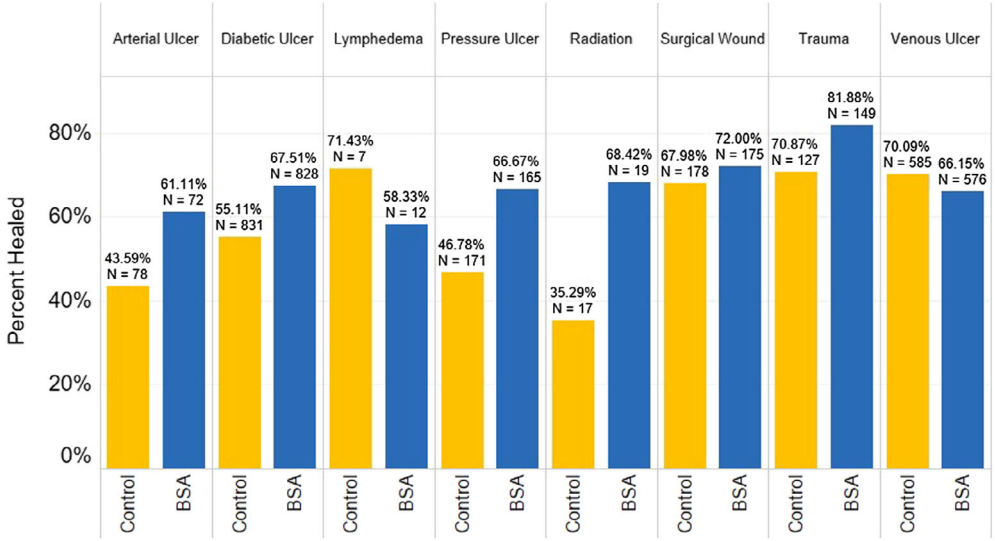

FIGURE 3 Modified intent-to-treat healing rates based on etiology

of healing by 0.44 (odds ratio 1.44, confidence interval [1.24, 1.66], $P < .001$). Hyperbaric oxygen therapy (HBOT) did not significantly influence the likelihood of healing, in isolation or in conjunction with BSA usage. The impact of negative pressure wound therapy was also considered, but no differences in utilisation were found that could have affected the study results. CPH analysis was performed, and although the model fits well ($P < .001$), the use of BSA did not significantly influence the time to heal (data not shown).

4 | DISCUSSION

Recent reporting of RCTs investigating the efficacy of CTPs has been increasingly limited to shallow wounds without deep structure involvement and of short duration. This is likely because of the increased complexity of trials that permit deeper wounds—for example, Wagner Grade 2, or stage 3 and 4 pressure injuries—requiring larger enrolment and longer study periods (eg, 16-24 weeks) to accommodate the slower wound-healing trajectories and complications that are inherent to these kinds of wounds. Such trials are, therefore, not only more costly and take a longer time to complete [20] but they are not generalisable to the real-world population because of the exclusionary criteria required in RCTs. The challenge is that clinicians, as well as payers who make coverage determinations, have little insight into which products are effective in the real-world setting, where medically complex patients present with severe wounds that are not simply DFU or VLU, but chronic ulcers that are a result of underlying comorbidities. This is especially true for wounds of multiple etiologies and of high severity (involving exposed deep structures). In other countries, and to some extent for trials involving other types of interventions, and for substantially older trials this is not true as can be seen by analysing recent reviews or systematic reviews.[21-23] Meta-analyses, in which data from numerous studies are combined to create a very

large pool of data, do not solve the problems created by RCT's because they typically draw from RCT's for data, and there may be significant variations in the treatment protocols from study to study that may further confound the results. Consequently, for payers relying on results from RCTs (the highest level of evidence) to construct coverage policies, there is a paucity of data that is directly applicable to the real clinical setting where patients frequently have significant comorbidities.

In cases where retrospective data are used, oftentimes, the CTP studies include small sample sizes not truly generalisable to the actual chronic wound-care population. Additionally, because this population generally presents with multiple underlying medical comorbidities, many are excluded from participation or are lost in follow-up. The methodology used to define the endpoints (eg, definition of healing) may not be consistent and the statistical methods used to create matched cohorts are not robust enough (eg, lack of propensity matching, etc) to yield nearly identical cohorts. An alternative is to consider well-conducted real-world evidence studies, which have been increasingly espoused as complementary evidence to RCTs, although the methods and rules by which such studies should be used as part of the evidence are still being debated.[24]

In this study, we used a database capturing data from more than 2 million patients to analyse and match data of 1997 complicated wounds of multiple etiologies that were treated with BSA plus SOC to a cohort of 1997 nearly identical patients who received SOC alone. The quality of this match was verified using a propensity score, which demonstrated no statistically significant differences between these cohorts, other than slight differences in the mean BMI and age. Furthermore, because the data was drawn from a large number of affiliated facilities, their treatment methodology for both SOC and BSA was very similar. This technique of propensity matching allows the investigators to identify matched pairs of subjects to make a strong comparison, without excluding patients because of the complexity of their wound. In this way, the authors believe that the current study design is a better reflection of treatment outcomes in the real world.

Using these matched pairs of subjects, the data demonstrated a statistically significant improvement in healing rates, PAR, amputations, recidivism, treatment completion, and medical transfers in those patients treated with BSA. Additionally, BSA significantly increases the odds of healing, regardless of the use of HBOT.

The difference between cohorts became more pronounced in the most complicated subjects, where exposed deep structures (muscle, tendon, and bone) were present. This is an important observation because most CTPs have only been studied in wounds without exposed structures. In this study, the overall healing rate for DFUs (67.5%) was well within the rates published from a Medicare claims analysis of the effectiveness of several CTPs,[25] confirming that our data are in the mainstream. More importantly, however, the mean number of applications of BSA (2.7) was substantially lower than that reported by Martinson and Martinson,[25] which ranged from 3.2 to 6.0. Fewer product applications can reduce acquisition costs and Medicare payment episodes, which may substantially provide better health economics implications for BSA in the treatment of diabetic wounds, regardless of the severity of the wound.

The wounds represented in this study were caused by a variety of factors and comorbid conditions and exhibited attributes that made their closure particularly challenging. Many of these wounds involved exposure of muscle, tendon, and bone. Historically, these have been difficult to close because of poor granulation and a lack of perfusion necessary to support the healing process. A previous study showed that bridging of these structures using BSA readily occurred.[9] The authors hypothesised that this finding could be attributed to BSA providing a collagen scaffold to enhance epithelial cell migration across the wound bed. Clinically, we have observed absorption of blood on contact with the wound bed. Therefore, the immediate perfusion of the graft is most likely attributed to the mature capillary network that exists already in the BSA. Consequently, the capillaries can facilitate absorption of blood and distribute it throughout the graft.

Prior to matching cohorts, we additionally observed that the subjects in the BSA cohort had more comorbidities than the population at large. This implies that clinicians tend to reserve BSA to treat patients with more complex wounds. Based on the findings presented herein, patients with complex wounds will benefit from early intervention using BSA.

One limitation of this study is that the wounds treated with BSA were often of higher severity, resulting in application later during the entire course of treatment. This may have potentially skewed healing rates and wound duration measures towards SOC. Another limitation is that the database does not include specific measures of vascularity or HbA1c, and this may have contributed to the differences in the healing rates observed.

A limitation that often exists in the registry data is that there may be variability in the data reported among the contributing clinics. Diagnoses or procedures may be subject to coding error, for which the extent of miscoding or undercoding that could result in bias is unknown, and may also result in measurement error in ICD-9/10 or CPT based variables. A benefit of selecting the 644 affiliated centers is that

it ensures consistency in reporting as well as the clinical practice.

The goal of this study was to evaluate the effectiveness of BSA for all wound etiologies in the real-world setting, where RCTs are impractical. Therefore, it was important to choose an EMR database where we could ensure standardisation of protocol-driven wound-care practices that include appropriate diagnosis, management, and documentation. Analyses using text fields instead of discrete numeric data may be subject to error resulting from incorrect interpretation of the data, which is why only data collected from discrete fields (not text fields) were considered. To overcome some of these limitations, only data from centers providing consistent and reliable EHR data were included to account for the challenges typically seen with the registry data. Additionally, the high volume of patient data and rigorous statistical methods used help overcome concerns of bias in results.

In conclusion, the study demonstrates that BSA is beneficial for treating wounds caused by a variety of etiologies and that BSA is particularly effective in the worst wounds, where exposed muscle, tendon, and bone are present. Most significantly, this real-world evidence further substantiates the current body of literature that until now has focused on head-to-head studies differentiating outcomes between CTPs and/or standard care through smaller RCTs in populations meeting stringent clinical trial exclusion criteria. Beyond demonstrating that use of a bioactive skin allograft achieves better outcomes than standard care alone, this study shows additional benefits including fewer amputations and medical transfers, lower recidivism, and higher treatment completion rates all within a significantly large medically complex patient pool representative of the true wound-care population and with volumes well beyond those reported through even the most robust meta-analyses.

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CONFLICT OF INTEREST

None noted.

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