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Predicting wound healing rates and survival with the use of automated serial evaluations of burn wounds☆

Bradley A. Rittenhouse[a,b], Julie A. Rizzo[a,b,*], Beth A. Shields[a], Matthew P. Rowan[a,1], James K. Aden[c], José Salinas[a], Craig A. Fenrich[a], Sarah K. Shingleton[a], Maria Serio-Melvin[a], David M. Burmeister[a], Leopoldo C. Cancio[a]

[a] United States Army Institute of Surgical Research, Fort Sam Houston,TX, United States
[b] Uniformed Services University of Health Sciences, Bethesda, MD, United States
[c] Brooke Army Medical Center, Fort Sam Houston, TX, United States

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ABSTRACT

Healing of burn wounds is necessary for survival; however tracking progression or healing of burns is an inexact science. Recently, the relationship of mortality and wound healing has been documented with a software termed WoundFlow. The objective of the current study was to confirm various factors that impact burn wound healing, as well as to establish a timeline and rate of successful healing. A retrospective analysis was performed on adults (n=115) with at least 20% TBSA burn that had at least two computer-based wound mappings. The % open wound (%OW) was calculated over time to document healing trajectory until successful healing or death. Only 2% of patients in the group with successful wound healing died. A decrease in the %OW of 0.8 (IQR: 0.7–1.1) was associated with survival. Disparities in wound healing trajectories between survivors and non-survivors were distinguishable by 2 weeks post-injury ($P < 0.05$). When %TBSA was stratified by decile, the 40–49% TBSA group had the highest healing rate. Taken together, the data indicate that wound healing trajectory (%OW) varies with injury severity and survival. As such, automated mapping of wound healing trajectory may provide valuable information concerning patient/prognosis, and may recommend early interventions to optimize wound healing.

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1. Introduction

The extent of burn injury is associated with a graded immune-inflammatory host response that results in physiologic derangements [1,2]. Percent total body surface area (% TBSA) burned, along with age and inhalation injury, are reported as primary determinants of mortality. Therefore, rapid wound healing after burn injury is considered essential for survival. The central role of the burn wound is evident with the adoption

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* *Corresponding author at*: United States Army Institute of Surgical Research, 3698 Chambers Pass, Fort Sam Houston, TX 78234, United States.
E-mail address: julie.a.rizzo.mil@mail.mil (J.A. Rizzo).
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of various practices that promote wound healing and prevent infection, which include early excision and autografting, enteral nutrition, and topical antimicrobial therapy [3–7]. Therefore, an objective tool that monitors open wounds and healing over time could inform providers of outcome expectations and help drive decisions surrounding treatment.

Both initial burn wound size and wound healing trajectory are important factors that determine survival. To address this clinical problem, the U.S. Army Institute of Surgical Research developed WoundFlow to monitor wound healing. WoundFlow is a digital wound mapping documentation software application used by clinicians to draw injury patterns on a standard, computerized Lund and Browder diagram. It provides a user-friendly, intuitive tool for mapping burns, soft tissue wounds, grafting procedures, and non-surgical treatments. The system has a back-end imagery database that associates mappings to specific dates, allowing providers to view wound healing progression over time. It also includes system analytics to track and measure wound healing progression using a variety of graphs and charts for the duration of patient hospitalization and after discharge. A previous study from our burn center demonstrated that WoundFlow was equivalent in accuracy to the paper Lund and Browder chart [8]. Another small study from our center examined the wound healing trajectory using WoundFlow and demonstrated that poor wound healing was associated with older age, higher body mass index (BMI), more frequent vasopressor utilization, and more frequent requirement for continuous renal replacement therapy (CRRT) [9].

These findings correlate with other studies on healing of burn and non-burn wounds, which show that older age, poor nutrition, infection, diabetes, peripheral vascular disease, uremia, liver failure, and malignancy are associated with decreased wound healing [10–12]. However, the potential of this software to identify acceptable wound healing rates remains to be examined. While it is entirely feasible that this software could be used to stratify acceptable outcomes, how quickly this could be done could realistically alter treatment strategy. As such, the goal of this study was to expand our current knowledge of the various factors that impact burn wound healing by re-evaluating these variables in a much larger group of burn patients whose wounds were mapped using the WoundFlow software. In addition, we aimed to use this software to identify if wound healing rates were different depending on extent of TBSA burned and how this was associated with survival. Ultimately, this information could be used to manage expectations of outcomes and treatments by establishing automated wound healing rates.

2. Methods

This study was conducted under a protocol approved by the institutional review board. A retrospective analysis of adults admitted to our burn center between April 2011 and March 2015 was performed. Inclusion criteria were at least 20% TBSA burn and presence of at least two computer-based wound mappings (including at least one mapping $\geq$14 days after injury). Subjects with limb amputations, those admitted more than one week after injury, and those with incomplete wound mappings were excluded.

Standard clinical practice during this time period included early excision and grafting, early and aggressive enteral nutrition, and frequent physical therapy. Inhalation injury was determined with fiberoptic bronchoscopy. CRRT was utilized for acute kidney injury (AKI). Total parenteral nutrition (TPN) was used only when patients were not able to tolerate enteral nutrition.

Demographic data collected from the electronic medical record included burn size, presence of inhalation injury, age, military or civilian affiliation, body mass index (BMI), and gender. Organ dysfunction data included use of vasopressors in the first 24 hours, ventilator days, use of CRRT, and use of TPN. The number of ventilator days was calculated by counting each calendar day as one day if at any point during that day the subject was on a ventilator. Outcomes of interest included mortality, the number of burn surgeries, ICU days, and hospital days.

WoundFlow software was utilized over the study period and allowed the clinician to label wounds on an electronic Lund and Browder diagram. Areas of the body were classified as one of the following: full thickness burns, partial thickness burns, unhealed donor sites, healed donor sites, burns with temporary wound coverage, burns with autograft coverage with open interstices, excised and open wounds, or healed wounds. Wounds covered with meshed autograft were mapped as healed when the interstices were fully epithelialized. (Fig. 1)

The % open wound (%OW) was defined as the % TBSA unhealed burn plus the % TBSA unhealed donor site, and was collected both from the computer-based burn mapping program and from the medical record as previously described [9]. The %OW was often greater than the % TBSA burn after the first excision and grafting, as it included both the unhealed burn and the unhealed donor site. Wound healing rates were defined as the average change in %OW per day (%OW/d). The overall healing trajectory started at the time of injury and continued until either healing was considered to be achieved (defined as %OW $<$ 10%) or the final mapping prior to death was performed (if healing was not achieved).

Statistics were performed using JMP® (Version 13.0.0. SAS Institute, Inc. Cary, NC) and included counts, percentages, median with interquartile range (IQR), ANOVA, linear regression, univariate analysis, and logistic regression. Subjects were separated into groups for analysis: those who healed vs. those who did not. Continuous variables were compared between groups of subjects using the Kruskal–Wallis test. Categorical variables were compared between groups of subjects using Chi-square or the Fisher's Exact test. All possible predictors of healing with $p < 0.10$ were included in the stepwise logistic regression. The least-significant factors were then removed one by one until the final logistic model included factors significantly associated with wound healing. Statistical significance was determined to be $p < 0.05$.

3. Results

One hundred and fifteen patients were included; 94 healed their wounds and 21 did not. These patients had a median of 8

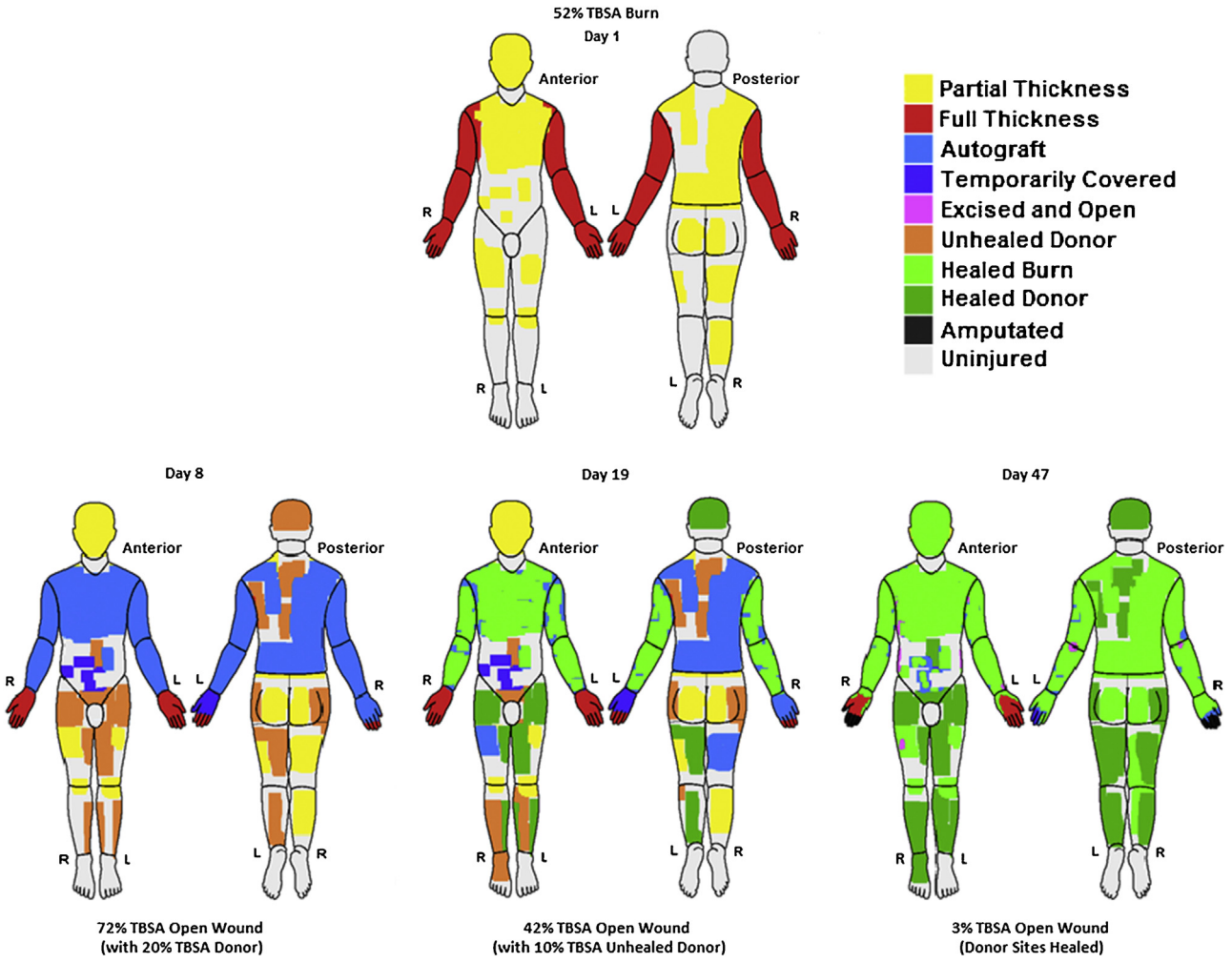

Fig. 1 – Wound flow diagram. Shown is an example of a patient who healed their wounds and survived on days 1, 8, 19, and 47.

(IQR: 6–14) computer-based wound mappings performed. Wound healing was associated with a 98% survival while failure to heal was associated with 100% mortality. Only two patients died after achieving wound closure. Patients who healed had a smaller burn size (30% TBSA IQR: 25–41 vs. 46% TBSA IQR: 30–66) and were younger (35 years IQR: 29–52 vs. 60 years IQR: 43–71), but did not differ with respect to BMI, gender, or the presence of inhalation injury (Table 1). From time of injury to healing, survivors demonstrated a decrease in %OW/d of 0.8 (IQR: 0.7–1.1). Fig. 2 shows the wound healing rate (%OW/d) stratified by %TBSA decile. Survivors with a burn size of 40–49% TBSA had the most rapid healing with median of 1.2% OW/d (IQR: 1.0–1.5). Patients who ultimately healed could be differentiated from those who would not by two weeks post injury (Fig. 3).

Univariate analysis demonstrated that wound healing failure was associated with a higher % TBSA burn, increased age, increased need for vasopressors in the first 24 h, more ventilator days, increased use of CRRT or TPN, and a greater number of burn surgeries. Those who failed to heal had a higher mortality and more ICU days but no difference in total hospital days (Table 2).

Table 1 – Baseline characteristics: healed vs. non-healed. N=number (count). %=percentage. IQR=Interquartile range. BMI=Body mass index. TBSA=Total body surface area.

Characteristic n (%) or median (IQR)	All (n=115)	Healed (n=94)	Non-healed (n=21)	p-value
SEX (women)	24 (21%)	20 (21%)	4 (19%)	1.000
Military	15 (13%)	14 (15%)	1 (5%)	0.169
Age (years)	36(IQR: 30-57)	35 (IQR: 29-52)	60 (IQR:43-71)	<0.001*
BMI (kg/m^2)	27(IQR: 23-31)	27 (IQR: 23-31)	27 (IQR: 23-31)	0.942
TBSA burn (%)	31(IQR: 26-46)	30 (IQR: 25-41)	46 (IQR:30-66)	0.002*
Inhalation injury	25 (22%)	19 (20%)	6 (29%)	0.413

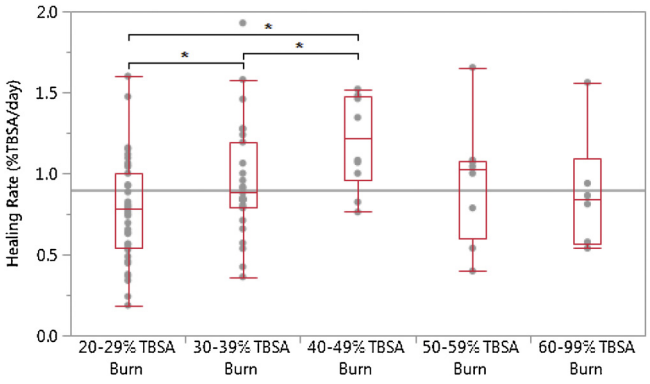

Fig. 2 – Wound healing rate (%OW/d) stratified by %TBSA decile reveals a significantly higher rate of wound healing for patients with 40–49% TBSA when compare to less extensive burns (*–$P < 0.05$).

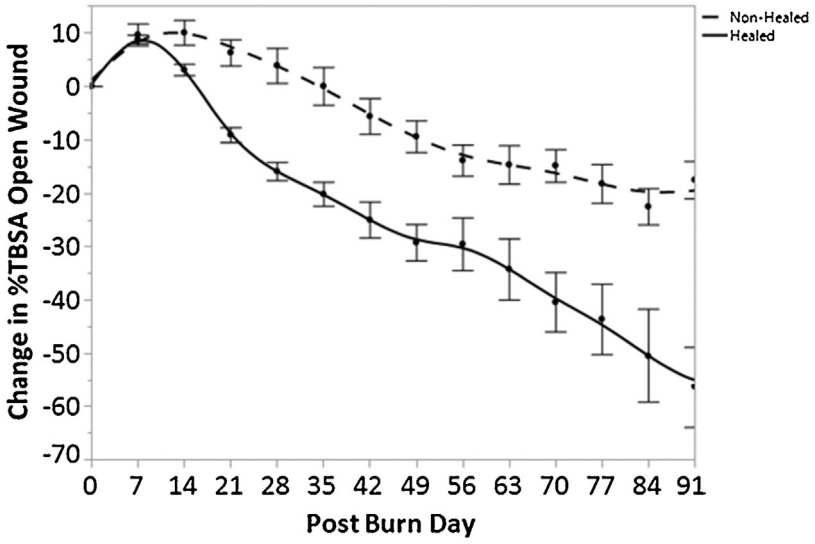

Fig. 3 – Change in %TBSA Open wound area over time reveals a divergence of wound healing rate between survivors and non-survivors by 2 weeks post-burn.

Table 2 – Treatments and outcomes: healed vs. non-healed. CRRT—continuous renal replacement therapy, TPN—total parenteral nutrition, ICU—intensive care unit.

Treatment n (%) or median (IQR)	All (n=115)	Healed (n=94)	Non-healed (n=21)	p-value
Use of vasopressors (first 24h)	55 (48%)	39 (41%)	16 (76%)	0.003*
Ventilator days	11 (IQR: 4-29)	9 (IQR:3-26)	26 (IQR:20-72)	<0.001*
Use of CRRT	33 (29%)	16 (17%)	17 (81%)	<0.001*
Use of TPN	26 (23%)	15 (16%)	11 (52%)	<0.001*
Number of burn surgeries	3 (IQR: 2-6)	3 (IQR: 2-5)	6 (IQR: 2-10)	0.034*
Outcome n (%) or median (IQR)				
Mortality	23 (20%)	2 (2%)	21 (100%)	<0.001*
ICU days	22 (IQR:14-46)	21 (IQR: 12-44)	27 (IQR: 21-90)	0.008*
Hospital days	37 (IQR: 28-62)	39 (IQR: 29-58)	27 (IQR: 21-90)	0.120

Multivariate logistic regression analysis was performed. The full model included all significant variables found significant in the univariate analysis, which initially included Age, TBSA burn (%), CRRT use, vasopressors in the first 24h, parenteral nutrition, ventilator days, and the number of burn surgeries. The final model included only % TBSA burn (OR- 1.086), increased age (OR- 1.108), and the use of CRRT (OR- 6.369), which were all independently, significantly associated with wound healing failure (Table 3).

Table 3 – Odds ratio estimations for wound healing failure. Odds ratios (OR) and confidence limits (CL) for variables found to be significant on univariate analysis. The final model reveals that age, TBSA (Total body surface area) and CRRT (Continuous renal replacement therapy) remain significant predictors of wound healing failure.

	Full model			Final model		
Effect	OR	95% Wald CL	p-value	OR	95% Wald CL	p-value
Age (years)	1.115	(1.045, 1.189)	<0.001*	1.108	(1.047, 1.172)	<0.001*
TBSA burn (%)	1.084	(1.024, 1.147)	0.001*	1.086	(1.034, 1.140)	<0.001*
CRRT	4.421	(0.795, 24.597)	0.090	6.369	(1.556, 26.064)	0.007*
Vasopressors in the first 24 h	1.550	(0.304, 7.913)	0.600	–	–	–
Parenteral nutrition	2.278	(0.468, 11.082)	0.308	–	–	–
Ventilator days	1.001	(0.972, 1.047)	0.638	–	–	–
Number of burn surgeries	1.023	(0.767, 1.245)	0.853	–	–	–

4. Discussion

This study confirmed that older age, higher % TBSA burn, and the presence of renal dysfunction (defined as need for CRRT) were associated with the failure to heal burn wounds. The WoundFlow software allowed us to determine that patients who healed their wounds did so at a median of 0.8%OW/d, with survivors of 40–49% TBSA burn healing the most rapidly at a median of 1.2%OW/d. The wound mappings obtained throughout the patients' hospital course demonstrated that patients who would ultimately heal could be differentiated from patients who would not heal by two weeks into their hospital stay and these rates continued to diverge after that time point.

The findings of this study—that older age and AKI requiring CRRT are associated with decreased wound healing correlate with other studies that examine factors affecting wound healing in both burn and non-burn populations [9,10,13–16]. Interestingly, the previous pilot study on WoundFlow did not identify % TBSA burn as a significant factor in achieving wound healing, as higher % TBSA burn is associated with increased mortality [17]. However, the current study does support the accepted concept that lower % TBSA burn is associated with improved outcomes. While this discrepancy can be partially explained by increased power in the current report, the previous pilot study also examined more severe injuries in an older patient population. In short, because of the association between wound healing and survival, it is not surprising that factors that affect mortality (e.g., age, %TBSA burned) also affect failure to heal wounds.

Another key difference between the current WoundFlow study and the pilot study was the impact of BMI with this study showing no difference in wound healing rate with respect to BMI while the prior pilot did. This finding reflects conflicting literature regarding the impact of obesity on burn patients' morbidity and mortality. Several studies implicate higher BMI to be responsible for lower functional outcomes [18] and higher mortality [19]. Other studies have suggested that obesity may be protective after burn injury [20]. While the groups in the current report had identical BMI values, it should be considered that the extent of obesity may affect interpretation of percentages used on Lund Browder diagrams. Automated imaging could easily be incorporated within the WoundFlow software, and should be examined in the future.

The definition of an ideal or calculated wound healing rate brings forth several potential uses. With this information, an expected length of stay could be calculated for a given patient with known age and %TBSA. As such, accurate estimates of their hospital length of stay could be given to family members and caretakers. Progress against this calculated length of stay could also be analyzed to give an idea of the progress of the patient, which would fine tune the expected prognosis. More realistic goals and expectations for the patient and their loved ones would improve overall care of the burn victim.

As the database of wound closure rates grows, this software may eventually be able to suggest whether a patient would be a candidate for advanced therapies not commonly employed. In this regard, certain technologies (e.g., xenotransplantation, tissue engineering techniques) may be examined when they otherwise may not. For example, a patient that reaches inadequate wound healing potential by the 2 week decision point may be a good candidate for novel skin substitutes or other more experimental techniques. Additionally, as resolution of the data improves, healing trajectories in different ages or %TBSA injuries gathered from this software will be gathered and may assist clinicians in making decisions regarding the patients' path to recovery. These possibilities will be the province of future work.

Limitations of this study include the subjective analysis of wound healing by the medical provider needed for completing the wound mappings. Current efforts aim to examine objective, non-invasive imaging techniques that could be incorporated into this software. Additionally, the small sample size prevented inclusion of a propensity analysis which would more ideally match patients in both groups in terms of age and TBSA. We did attempt this analysis, and included it as a supplemental table which led to a sample size of 22 and 12 in the non-healed group for all patients and only those who survived, respectively. Clearly, not all factors that potentially contribute to wound healing were examined in this study, and future research will endeavor to build a more comprehensive database of variables associated with healing.

5. Conclusion

Wound healing trajectory may provide an additional clue as to a patient's status, and can prompt early investigation or

interventions to optimize wound healing. Also, large burn size, older age, and the development of AKI should trigger heightened vigilance to wound healing status. These parameters are traditionally associated with mortality, although they are also associated with wound healing failure. Well-defined acceptable rates of wound healing would allow for novel and extreme therapeutic interventions, and may inform the strategy of excision and grafting for certain patient populations.

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved experimental animals has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.burns.2018.10.018.

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