Original Article

Clinical Parameters Associated With Pressure Ulcer Healing in Patients With Advanced Illness

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Abstract

Context. Pressure ulcers are the most prevalent wounds affecting patients with advanced illness. Although complete wound healing is the most desired outcome, it remains unlikely in the setting of patients with limited life expectancy. Realistic goal setting may be enabled using objective clinical parameters.

Objectives. To identify clinical parameters associated with complete healing of Stage II pressure ulcers.

Methods. Univariable and multivariable competing risk analyses were used to assess the association of complete healing with the following six clinical parameters, namely gender, age, total number of pressure ulcers, total number of other wounds, number of failing organ systems, and Palliative Performance Scale (PPS) scores.

Results. A total of 147 patients with 245 Stage II pressure ulcers were followed until death; 9.4% of Stage II pressure ulcers achieved complete healing. Univariable analyses showed hazard ratios (HRs) for complete healing in favor of higher levels of PPS scores (HR 1.82−5.99, $P < 0.001$) and age younger than 80 years (HR 3.28, $P = 0.031$). Multivariable analyses showed HRs for complete healing in favor of higher levels of PPS scores (HR 1.49−3.34, $P = 0.003$).

Conclusion. Higher levels of PPS scores are associated with complete healing of Stage II pressure ulcers in patients with advanced illness.   J Pain Symptom Manage 2014;47:1035−1042. © *2014 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Pressure ulcer, advanced illness, palliative care, wound healing, wound management, Palliative Performance Scale

Introduction

Patients with advanced illness represent the cohort within health care experiencing the highest overall prevalence and incidence of all wound classes.[1−3] A recent prospective study reported

that almost two-thirds of patients presented with at least one wound and an average of 1.8 wounds per patient on referral to a regional tertiary palliative care program.[1] In addition, patients developed an average of 1.5 wounds between referral and death.[1] The most prevalent wound class is pressure ulcers, affecting about one-fifth of the patients with advanced cancer and about two-thirds of advanced noncancer patients.[1–3]

Wound management espouses multiple goals including wound healing, wound palliation (palliative wound care or wound-related pain and symptom management), and wound prevention (primary and secondary wounds as well as prevention of wound-related complications such as infection).[4–8] Although the prime and most fundamental goal is complete wound healing, this is not always possible, given the limited life expectancy of patients with advanced illness.[4–8] Moreover, goals of wound management change over a patient's lifespan.[4–8] When a patient is young and healthy, wounds have the greatest potential and likelihood to completely heal. However, as a patient becomes increasingly elderly, progresses to advanced illness, and approaches end of life, complete healing becomes less likely. Therefore, realistic goals of care must be formulated and negotiated with the patient, along with the development of appropriate treatment plans.

The ability to more accurately and objectively predict the likelihood of complete healing of a given wound may be useful in the process of formulating realistic goals of care together with appropriate treatment plans. This study aims to look at clinical parameters that are gleaned in a noninvasive manner, at the patient's bedside. Equipped with data pertaining to such clinical parameters, clinicians may have more thorough discussions with patients and/or their substitute decision makers around potential outcomes, goals of care, expectations, and appropriate treatment modalities.

Methods
Study Design
This was a prospective analysis of patients referred to a regional palliative care program in Toronto, Canada. The palliative care program comprises a home consultative service with linkages to a palliative care inpatient unit and an associated hospital-based palliative consultative service. Collectively, the combined community- and hospital-based components serve an estimated population of 750,000 within the northwest quadrant of metropolitan Toronto. Recruitment for this study was commenced with new referrals on May 1, 2005 and ended on June 30, 2006. The study protocol was approved by the research ethics board at the William Osler Health System in Toronto, Canada.

Patients
All patients were referred for consideration of supportive and palliative care. Referrals were received from primary care physicians, oncologists, internists, and surgeons. All patients or their substitute decision makers provided consent to have their clinical data registered in a research database. Patients were followed until their deaths except for a small number who were discharged from the program. The focus of this study was patients with advanced illness, defined as patients who are expected to die within six months of referral. All patients were examined within 24 hours of the initial referral. Data collected were entered in a customized Microsoft Corporation™ Access database by all research collaborators on an accrual basis. Patients were followed by serial clinical assessments throughout their palliative care trajectory, culminating in their death either in the community or the hospital. Performance status was measured at initial referral (baseline) using the Palliative Performance Scale (PPS) Version 2.[9] Risk for the development of pressure ulcers was measured using the Braden Scale.[10] Pressure ulcers were classified according to the system developed by the National Pressure Ulcer Advisory Panel.[11] Given that the data were collected before 2007, the new stage termed "deep tissue injury" was not used. The research team classified pressure ulcers as Stages I, II, III, IV, and unstageable. All wounds were managed by a specialist wound management team consisting of a specialist wound physician and advanced practice nurse and were managed using the fundamentals of the wound bed preparation paradigm as per Falanga,[12] Sibbald et al,[13] and Schultz et al.[14] Thus, all wounds were given treatment with the intent to heal and records were kept of complete healing. In addition,

wound-related pain and symptom management (wound palliation) followed best practice guidelines.[15] Complete healing was defined as complete wound closure together with the restoration of complete epithelialization over a former wound site.

This study focuses on Stage II pressure ulcers present at the time of referral to the program. According to the National Pressure Ulcer Advisory Panel, Stage II pressure ulcers represent full thickness loss of epithelium with subtotal loss of dermis.[11] The resolution of Stage I lesions was not analyzed as there is low inter-rater agreement for the solely clinical (nontechnologic) assessment of Stage I lesions, especially in non-Caucasian patients.[16−18] Furthermore, Stage I lesions do not present with loss of epithelium, thus making it of dubious value to look for predictors of healing for this group. Because none of the Stage III, IV, or unstageable pressure ulcers healed completely, it was not feasible to study factors related to their healing.

Statistical Analysis

Through a review of the literature and personal experience, the following six variables were chosen as potential predictors of Stage II pressure ulcer complete healing: the patient's total number of pressure ulcers of all stages, the patient's total number of wounds from other classes (malignant wounds, skin tears, venous leg ulcers, diabetic foot ulcers, and arterial leg/foot ulcers), gender, age, the PPS score of the patient on admission, and the number of the patient's organ systems (heart, lung, renal, brain, and liver) that were failing. The following are the examples of various component types of organ system failure: heart (congestive heart failure, recent myocardial infarction, or severe valvular heart disease), lung (pulmonary fibrosis or chronic obstructive pulmonary disease), renal (diabetic nephropathy, ischemic nephropathy, renal transplant rejection, or polycystic disease), brain (all dementias, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, recent brain hemorrhage, or thromboembolic stroke), and liver (all forms of cirrhosis or active hepatitis). Gender (male or female), race (Caucasian or other), and age (<80 or 80+ years) were categorical; the rest of the variables were treated as continuous because monotonic relationships were expected and using continuous variables greatly reduced the number of

variables needed, a concern because there are relatively few healing events in the sample and overfitting can become a problem. A recent study demonstrated that it is reasonable, and indeed preferable, to use PPS as a continuous variable in prognostic models as it explained 34.7% of the variation in survival times of patients with advanced illness vs. only 24% explained by the two-category variable (unpublished data; available from the corresponding author).

The relationships between the explanatory variables and time to wound healing or death were explored by plotting individual cumulative incidence functions that show the probability of complete healing before death and of the competing risk of dying before complete healing. Uni- and multivariable modeling of the time to complete healing was done using the competing risks survival model of Fine and Gray,[19] in which the exponent of a coefficient can be interpreted as the hazard ratio (HR) of the subdistribution. Modeling was done in the statistical software R.[20] To accommodate the potential correlation caused by some patients contributing more than one Stage II pressure ulcer to the outcomes, the sandwich estimator of variance in the *coxph* function from the survival package[21] was used, after the data were prepared for competing risk analysis by using the *crprep* function in the mstate package.[22]

Results

A total of 607 patients were enrolled during the recruitment period. All patients were followed until their deaths except for 57 who were discharged from the program and who are excluded from our analysis. The most common reasons for discharge were transfers to other hospitals, hospices, or nursing homes (NHs). Of them, 147 patients presented with Stage II pressure ulcers. The primary diagnosis for 53 patients was cancer, whereas 94 had a primary noncancer diagnosis. Patient characteristics are given in Table 1. A total of 245 Stage II pressure ulcers were monitored in this study. Complete healing was documented for 23 (9.4%) Stage II pressure ulcers.

Cumulative incidence functions of the probability of complete healing before death of Stage II pressure ulcers and of the competing risk of dying before complete healing is shown

Characteristics of 147 Patients With Stage II Pressure Ulcers Present at Referral

Characteristics	n (%)
Gender	
Male	65 (44.2)
Female	82 (55.8)
Race	
Caucasian	119 (81.0)
Hispanic	2 (1.4)
Black	10 (6.8)
Asian	4 (2.7)
South Asian	12 (8.2)
Age (y)	
<60	7 (4.8)
60–79	58 (39.5)
80+	82 (55.8)
PPS score	
10	29 (19.7)
20	39 (26.5)
30	47 (32.0)
40	15 (10.2)
50	11 (7.5)
60	5 (3.4)
70	1 (0.7)
Number of failing organ systems per patient	
0	3 (2.0)
1	84 (57.1)
2	46 (31.3)
3	14 (9.5)
Total number of pressure ulcers of any stage per patient	
1	25 (17.0)
2	44 (29.9)
3	26 (17.7)
4	28 (19.0)
5+	24 (16.3)
Total number of nonpressure ulcer wounds per patient	
0	85 (57.8)
1	31 (21.1)
2	20 (13.6)
3+	11 (7.5)

PPS = Palliative Performance Scale.

in Fig. 1. The figure suggests that younger age and higher PPS score and perhaps fewer other wounds and fewer organ failures may be associated with both complete healing before death and with longer survival.

In univariable Fine and Gray models (Table 2), the hazard of healing (note: the term hazard here is technical and not meant in a negative sense) was significantly greater for younger patients (HR 3.28 for age <80 vs. 80+, $P = 0.031$) and for those with higher PPS scores (HR 1.82–5.99, $P < 0.001$), and was borderline significant for number of other wounds (HR 1.79–3.21, $P = 0.053$) and number of failing organ systems (HR 2.21–4.86, $P = 0.063$). When all the variables were entered in a multivariable model, PPS score remained significant (HR 1.49–3.34, $P = 0.003$).

Discussion

This is the first prospective study that specifically focuses on patients with advanced illness referred for supportive and palliative care. Thus, the study population being considered is more homogeneous and uniform with regard to patient characteristics, philosophy of care, and prognosis. The currently available literature contains studies that look at patients in specific care settings such as NHs, long-term care facilities (LTCs), and intensive care units. The patients with advanced illness reside within any of the aforementioned settings; however, they are mixed with other patients who are not necessarily facing a limited life expectancy and may be receiving a care plan that is neither aligned nor congruent with supportive and palliative care.

Our study showed that 9.4% of Stage II pressure ulcers achieved complete healing among a cohort of terminally ill patients, with less than six month life expectancy, referred for supportive and palliative care. Although this level of complete healing may seem trivial, it is nonetheless a remarkable achievement as it occurred in the context of patients with progressively deteriorating status. Unfortunately, within this cohort, there was zero complete healing of pressure ulcers that were Stages III, IV, and unstageable. Thus, although it may be possible to regenerate epithelial and dermal elements within a shortened life expectancy, it requires much more time to regenerate connective tissues (fat, fascia, tendons, and ligaments), muscle, and bone. A retrospective study of 1241 Stage II pressure ulcers among 774 NH patients showed complete healing of 563 (45.4%) lesions.[23] However, only 75 (9.7%) of those NH patients died, reflecting that they were much healthier than the patients within our study.[23]

This study is the first to show that the most robust clinical parameter associated with complete healing of Stage II pressure ulcers affecting patients with advanced illness is their PPS score. As a globally used assessment tool, the PPS generates a composite score that
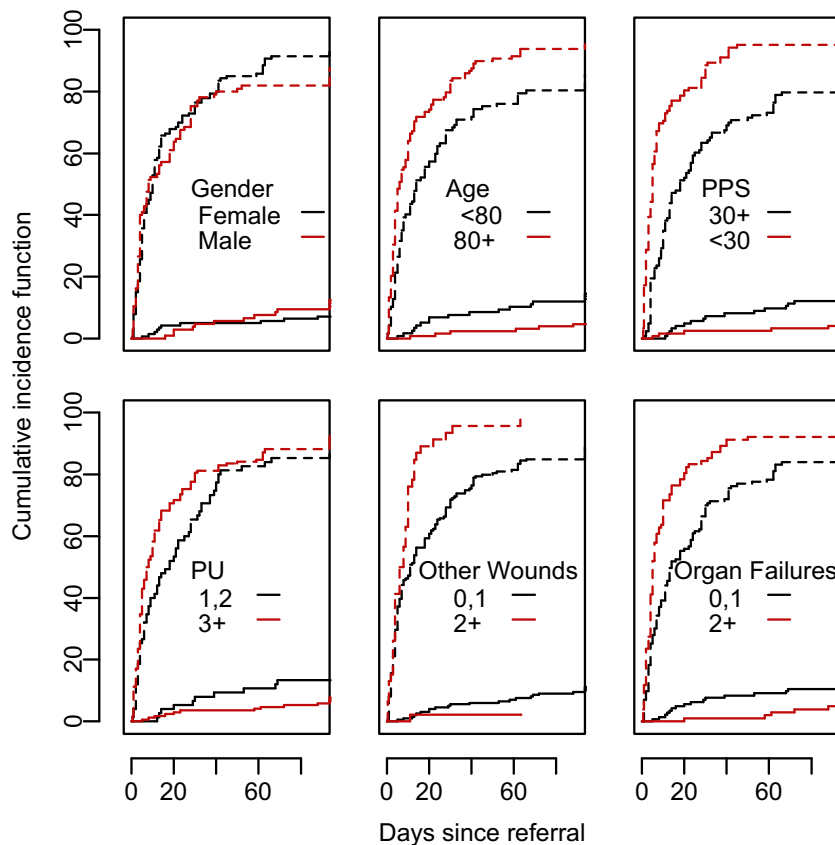
Fig. 1. Cumulative incidence functions showing the probability of complete healing before death of Stage II PUs (solid lines) and of the competing risk of dying before complete healing (dashed lines), for gender, age, PPS score, total number of PUs, number of other wounds, and number of failing organ systems. PPS = Palliative Performance Scale; PU = pressure ulcer.

equates to a summation of the following six different patient features: ambulation, activity, evidence of disease, self-care, intake, and level of consciousness.[9] Thus, the PPS reflects overall disease burden and the end results of all comorbid processes. A recent meta-analysis has shown that the PPS is highly correlated with survival predictions in both advanced cancer and advanced noncancer illnesses.[24] Moreover, changes in a patient's PPS score represent additional independent predictors of survival.[25] Furthermore, because the PPS has such a high level of correlation ($r = 0.885$, $P < 0.001$) with the Braden Scale, it may be used as a proxy for assessing risk of developing pressure ulcers.[26] Thus, our results are consistent with results from retrospective studies in NH and LTC settings that correlate complete healing of pressure ulcers with longer survival, increased mobility, and bowel/bladder continence.[27,28]

Younger age (<80 vs. 80+ years) showed a statistically significant association with complete healing of Stage II pressure ulcers in the univariable model (HR 3.28, $P = 0.031$). However, it did not achieve statistical significance in the multivariable model (HR 2.33, $P = 0.117$). Although intuitively one would expect that advanced age would be associated with reduced capacity to heal, three retrospective studies from the NH and LTC settings show no association between age and complete healing.[29−31]

The two factors that were marginally significant in univariable models (number of other wounds and number of failing organ systems) were not significant in the multivariable model. This is not because they are unimportant but because they are correlated with PPS score, which is the stronger predictor, and once one adjusted for PPS score, they do not add significantly to the model. Considered on their own,

Parameters	Univariable Model				Multivariable Model			
	Coefficient	HR for Healing	Robust SE	P-Value	Coefficient	HR for Healing	Robust SE	P-value
Gender								
Female vs. male	−0.55	0.58	0.501	0.271	−0.14	0.87	0.492	0.776
Age								
<80 vs. 80+	1.19	3.28	0.552	0.031	0.84	2.33	0.539	0.117
Number of pressure ulcers in total (continuous)								
2 vs. 1	−0.14	1.15	0.114	0.219	−0.08	1.08	0.079	0.340
3 vs. 1		1.32				1.16		
Number of other wounds (continuous)								
1 vs. 0	−0.58	1.79	0.301	0.053	−0.49	1.63	0.322	0.127
2 vs. 0		3.21				2.67		
Number of failing organ systems (continuous)								
1 vs. 0	−0.79	2.21	0.425	0.063	−0.29	1.33	0.329	0.380
2 vs. 0		4.86				1.78		
PPS score (continuous)								
20 vs. 10	0.06	1.82	0.013	<0.001	0.04	1.49	0.013	0.003
30 vs. 10		3.30				2.23		
40 vs. 10		5.99				3.34		

HR = hazard ratio; SE = standard error; PPS = Palliative Performance Scale.
[a]Determined using competing risks modeling. Robust SEs were used to accommodate multiple pressure ulcers per patient.

however, this study demonstrated that a lower number of wounds from other classes correlated with the complete healing of Stage II pressure ulcers in the same patient. Although the reasons for this occurrence are not immediately clear, one may postulate that wounds such as arterial ulcers, venous ulcers, and malignant wounds are driven by different pathophysiologic mechanisms that additionally impede the healing of pressure ulcers. At present, there are no other studies that have looked at this particular issue. Similarly, the greater the burden of other organ system failure likely impacts on the integrity of the body's largest organ, namely the integument system. A retrospective study of Stage II pressure ulcers among NH patients did not show any statistically significant associations between complete wound healing in the setting of heart failure and/or renal failure.

Our study is not without limitations. First, it involved a single site and studied a relatively small cohort of patients. Second, the cohort size was not large enough to be able to study the capacity for complete healing of higher stages of pressure ulcers. Finally, the results also may be subject to confounding as the investigators did not use deep tissue injury within their classification. Although our study did not consider the effect of wound size, five retrospective studies conducted in the NH and LTC settings showed an association between complete healing and smaller wound area and smaller wound depth.[23,27,30,32,33]

Conclusion

Although complete healing of pressure ulcers remains an unlikely event among patients with advanced illness, marginal levels of healing may still occur. The ability to draw on clinical parameters that are easily and readily available at the patient's bedside, in a noninvasive fashion and at no additional cost, represents a clear advantage. Using the clinical parameters identified in this study may help clinicians to discuss realistic goals of care along with appropriate treatment plans. This study demonstrates the value and utility of the PPS in assessing the potential for healing of pressure ulcers among patients with advanced illness. Thus, the PPS may be considered as a key prognostic tool for both "quoad vitam" (prediction of life expectancy) and "quoad sanantionem" (prediction of healing capacity)

in patients with advanced illness.[34] Future studies should avoid looking at heterogeneous care settings such as NHs, LTCs, or intensive care units, and focus on cohorts of patients that are homogeneous in terms of patient characteristics, prognosis, and philosophy of care. In addition, future research also should consider biochemical, hematologic, and other laboratory investigations for potential associations with wound healing. Finally, given the marginal levels of healing among patients with advanced illness, greater emphasis must be given to the prevention of pressure ulcers and optimizing wound palliation.

Disclosures and Acknowledgments

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