A Predictive Model of Recurrent Lower Extremity Cellulitis in a Population-Based Cohort

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Background: Cellulitis is common and recurs in some patients. The study described herein derived a predictive model for the recurrence of lower extremity cellulitis in a population-based cohort.

Methods: We conducted a retrospective, population-based cohort study using the Rochester Epidemiology Project. We reviewed the medical records of Olmsted County, Minnesota, residents with lower extremity cellulitis occurring from January 1, 1999, to June 30, 2000. Univariate and multivariate Cox proportional hazards analyses were performed to evaluate risk factors in patients who experienced recurrent lower extremity cellulitis within 2 years. A predictive model was developed to estimate risk of recurrence based on a score of risk factors identified by multivariate analysis.

Results: A total of 209 episodes met the definition of lower extremity cellulitis. Thirty-five patients (16.7%) experienced recurrence within 2 years. Multivariate analysis identified tibial area involvement, prior malignancy, and dermatitis affecting the ipsilateral limb as independent risk factors for recurrence, with hazard ratios of 5.02, 3.87, and 2.99 ($P<.01$), respectively. A score calculated from these variables (a count of 0, 1, 2, or 3) was developed to measure risk of recurrence. Based on the predictive model, the estimated probability of recurrence (95% confidence interval [CI]) within 2 years was 5.0% (95% CI, 1.6%-8.2%), 17.3% (95% CI, 11.1%-23.0%), 50.6% (95% CI, 34.2%-63.0%), or 92.8% (95% CI, 51.9%-98.9%) for a score of 0, 1, 2 or 3, respectively.

Conclusions: We derived a model including tibial area involvement, history of cancer, and dermatitis to predict recurrence of lower extremity cellulitis. Potential interventions can be incorporated into treatment to diminish the proclivity for recurrence in high-risk patients.

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RISK FACTOR ANALYSES HAVE been performed[1-3] to better understand the pathogenesis of lower extremity cellulitis so that high-risk patients can be identified and potential interventions can be incorporated into treatment to attempt to diminish the proclivity for infection recurrence. A consistent theme demonstrated in the 3 surveys[1-3] is that local factors, including leg edema, tinea pedis, or other chronic dermopathies, and history of cellulitis, are prominent among identified risk factors. These identified risk factors by statistical evaluation are congruous with our long-standing clinical observations. In 1 of the 3 investigations,[3] an analysis of risk factors for recurrence of lower extremity cellulitis was performed. Prior leg surgery, other than saphenectomy, was identified as a risk factor associated with recurrent disease among a hospitalized cohort of patients.

To our knowledge, this is the first published population-based study of risk factors for recurrent lower extremity cellulitis. We therefore conducted a population-based cohort study of lower extremity cellulitis. We aimed to derive a predictive model for the development of recurrent lower extremity cellulitis.

METHODS

STUDY POPULATION

The study population of Olmsted County, Minnesota, consists largely of middle-class white individuals with characteristics similar to those of the general US non-Hispanic white population.[4] Physicians participating in the Rochester Epidemiology Project (REP) are from include nearly all Olmsted County health care hospitals and clinics, including the Mayo Clinic and Olmsted Medical Center (Rochester) and physicians' private practices. The institutional review boards of the Mayo Clinic and Olmsted Medical Center approved the study for REP use. Residents of Olmsted County who participate in the REP provide consent for use of their medical records in epidemiologic research.

STUDY DESIGN

The study was a retrospective inception cohort of patients with a first episode of lower extremity cellulitis. The cohort was followed

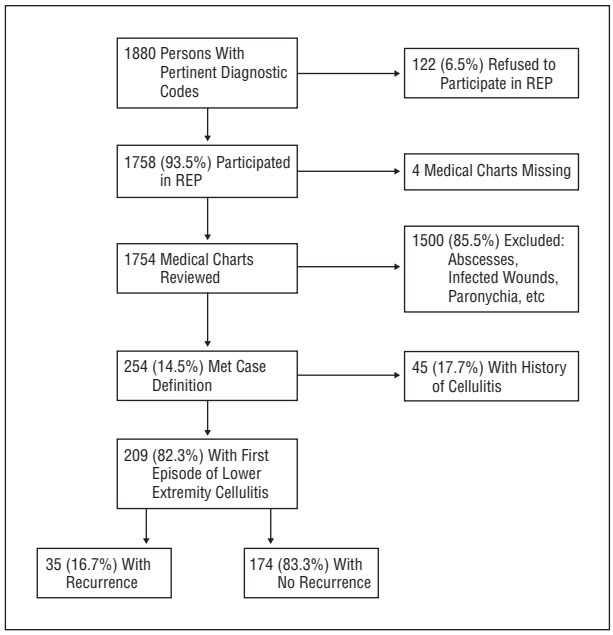

Figure 1. Study flow diagram of lower extremity cellulitis. REP indicates Rochester Epidemiology Project.

for 2 years after diagnosis to determine if any patient developed recurrent lower extremity cellulitis. Risk factors for recurrence were examined. Identification of cases was based on the review of medical indexing codes consistent with possible cellulitis combined with medical record review to ascertain the diagnosis based on a case definition of lower extremity cellulitis and subsequent recurrence of cellulitis within 2 years of the initial cellulitis episode.

CASE ASCERTAINMENT

Patients were identified through medical indexing of the centralized database of the REP as outlined in our earlier work (unpublished observations). We identified possible cases of lower extremity cellulitis occurring between January 1, 1999, and June 30, 2000, which is the most recent period for which trained nurse abstractors have verified computer-generated diagnostic codes in the REP database. Individuals with *International Classification of Diseases, Ninth Revision (ICD-9)*[5] diagnostic codes for lower extremity cellulitis and abscess (*ICD-9* codes 681.1, 682.6, and 682.7; *Hospital Adaptation of the International Classification of Diseases*[6] [*HICDA*] codes 06819111, 06819114, 06819120, 06824, and 06825), cellulitis not otherwise specified (*ICD-9* code 682.9, *HICDA* code 06829), erysipelas (*ICD-9* code 035, *HICDA* code 06863), and recurrent cellulitis (*HICDA* code 06829130) were identified.

Medical records of possible cases were reviewed by the principal investigator (D.R.M.) to ascertain the diagnosis of lower extremity cellulitis and the presence of a subsequent episode of cellulitis within 2 years of the initial episode. Uncertainties in classification were reviewed with an experienced investigator (L.M.B.). In a blinded fashion, 2 investigators (E.F.B. and L.M.B.) independently reviewed and classified a 5% randomly selected sample of total possible cases to assess the reliability of the case-classification procedure.

CASE DEFINITION

Our case definition is consistent with clinical research[7] and treatment guidelines,[8] both as the acute development of an expanding area of warm, erythematous skin with local edema that occurred on a lower extremity below the buttocks and as consistent with skin infection. Fever and local pain were not necessary to meet the case definition. The predominant anatomic site (femoral area, tibial area, or foot) of involvement was recorded. Patients seen at any health care facility, including ambulatory clinics, nursing homes, emergency departments, and hospital wards, were included. A recurrence of lower extremity cellulitis was defined as a second episode of cellulitis meeting the case definition at the same anatomic site (occurring at least 1 month after initial diagnosis) within 2 years of the initial episode. This must have occurred after the previous episode had been considered to have been successfully treated, either by follow-up documentation in the medical record or by absence of any medical record documenting failure of therapy of the initial episode. Extension of, or changing of, antimicrobial therapy for worsening or persistence of cellulitis while a patient was receiving therapy for the initial episode did not count as a recurrent episode of cellulitis.

Noninfectious conditions and other syndromes of skin and soft tissue infection were excluded. The excluded infections were secondarily infected primary dermatologic processes, folliculitis, paronychia, erythema overlying septic bursitis, septic arthritis or osteomyelitis, skin infection in the neutropenic host, infection complicating severe soft tissue injury, fasciitis or myositis, carbuncles, furuncles, and infected wounds (including surgical site infections, bite wounds, lacerations, punctures, abrasions, and infected ulcers).

Dermatitis was defined as physician-diagnosed dermatitis (including stasis dermatitis, eczema, and psoriatic plaques) present on the ipsilateral lower extremity at the time of evaluation of the initial episode of lower extremity cellulitis. History of malignancy was defined as documentation in the medical record of physician-diagnosed malignancy (excluding superficial dermatologic malignancy).

STATISTICAL ANALYSIS

Baseline characteristics, comorbidities, and other prognostic factors were compared between recurrent and nonrecurrent cellulitis cases by using statistical tests and regression modeling. For univariate analyses, differences between the 2 groups were assessed using tests based on the variable type. For categorical variables, a χ^2 test for association was used, unless counts were small when the Fisher exact test was employed. Continuous variables were examined for statistical differences with a 2-sample *t* test if normality assumptions were met; otherwise, the nonparametric alternative Wilcoxon rank sum test was used. Each variable was then tested for an association with time to recurrence using Cox proportional hazards regression modeling. Model results, including hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values, are presented to show the magnitude and significance of each variable as it relates to risk of recurrence. A multivariate model was constructed based initially on univariate findings and then refined using forms of stepwise selection. The statistical cutoff point for entry was 0.2 and for removal was 0.10. Bootstrap resampling was performed to validate the results of the multivariate analysis.[9] Kaplan-Meier survival curves were created, and comparisons were assessed based on presence or absence of certain risk factors. A significance level of $P<.05$ was used for all testing.

PREDICTION MODEL

A score-based predictive model for recurrent cellulitis was developed from the Cox proportional hazards multivariate model using a regression coefficient–based scoring method.[10] To generate a simple integer-based point score for each predictor vari-

Table 1. Comparison of Clinical Characteristics of the 2 Study Cohorts With Lower Extremity Cellulitis*

Variable	No Recurrence (n = 174)	Recurrence (n = 35)	*P* Value†	Univariate HR (95% CI)‡
Age, mean ± SD at incident event, y	57.9 ± 20.6	70.3 ± 20.5	.002	1.36 (1.13-1.63)§
Sex				
Female	93 (53)	22 (63)		1 [Reference]
Male	81 (47)	13 (37)		0.69 (0.35-1.36)
Weight, kg	89.8 ± 26.8	90.2 ± 40.6	.28	1.00 (0.99-1.01)
Height, cm	168.5 ± 10.3	164.2 ± 11.2	.04	0.45 (0.23-0.88)‖
BMI	31.7 (8.9)	32.3 ± 11.4	.73	1.01 (0.97-1.05)
Temperature, °C	36.9 ± 0.8	37.1 ± 1.1	.15	1.43 (0.97-2.11)¶
WBC count, $\times 10^9$/L	10.4 ± 4.3	11.0 ± 5.2	.63	1.03 (0.93, 1.14)
Treatment with antibiotic drug therapy				
IV antibiotic therapy, d	1.1 ± 2.5	1.1 ± 1.5	.27	1.00 (0.87-1.14)
Oral antibiotic drug therapy, d	9.2 ± 3.8	9.6 ± 2.8	.48	1.03 (0.95-1.12)
Total antibiotic drug therapy, d	11.4 ± 5.8	12.2 ± 6.4	.48	1.02 (0.97-1.08)
Hospitalization	39 (22)	12 (34)	.14	1.79 (0.89-3.61)¶
Hospitalization, length of stay, d	3.4 ± 3.1	4.8 ± 9.0	.51	1.04 (0.95-1.13)
Extension of antibiotic therapy	26 (15)	7 (20)	.47	1.28 (0.56-2.93)
Mortality: prior to 2 y of follow-up	18 (10)	4 (11)	.85	1.76 (0.62-5.04)
Blood cultures positive for a pathogen	4 (2)	2 (6)	.27	2.37 (0.57-9.88)
Charlson Index, severity weighted sum	1.8 ± 2.7	2.1 ± 2.8	.28	1.04 (0.94-1.17)
Alcohol dependence	10 (6)	1 (3)	.48	0.52 (0.07-3.80)
Diabetes mellitus	28 (16)	7 (20)	.57	1.29 (0.56-2.95)
Congestive heart failure	21 (12)	4 (11)	.92	1.05 (0.37-2.97)
History of cancer	12 (7)	8 (23)	.003	3.27 (1.48-7.21)§
Tobacco abuse	23 (13)	2 (6)	.21	0.44 (0.11-1.83)
History of contralateral leg cellulitis	11 (6)	4 (11)	.29	1.84 (0.65-5.22)
History of ipsilateral leg DVT	6 (3)	2 (6)	.52	1.66 (0.40-6.93)
History of contralateral leg DVT	5 (3)	0 (0)	.31	∟
Chronic lower extremity edema	56 (32)	22 (63)	<.001	3.52 (1.77-7.00)§
Venous insufficiency	33 (19)	18 (51)	<.001	3.88 (2.00-7.54)§
Arterial insufficiency	9 (5)	1 (3)	.56	0.65 (0.09-4.78)
Saphenous venectomy	7 (4)	0 (0)	.23	∟
Lymph node dissection	2 (1)	1 (3)	.44	2.98 (0.41-21.84)
Tinea pedis	35 (20)	9 (26)	.46	1.31 (0.62-2.80)
Onychomycosis	32 (18)	13 (37)	.01	2.28 (1.15-4.54)‖
Lower extremity ulcer	8 (5)	4 (11)	.11	2.81 (0.99-7.99)‖
Minor trauma preceding cellulitis	8 (5)	5 (14)	.03	2.93 (1.14-7.56)‖
Ipsilateral leg dermatitis	17 (10)	14 (40)	<.001	4.42 (2.25-8.71)§
Ipsilateral leg prosthetic joint	12 (7)	4 (11)	.36	1.74 (0.61-4.93)
Total knee arthroplasty	8 (5)	3 (9)	.34	1.88 (0.58-6.15)
Total hip arthroplasty	4 (2)	1 (3)	.84	1.33 (0.18-9.74)
Ipsilateral leg Fx or orthopedic surgery	21 (12)	3 (9)	.55	0.71 (0.22-2.33)

(continued)

able, scores were assigned by dividing β coefficients by the absolute value of the smallest coefficient in the model and rounding to the nearest integer. The overall risk score was calculated by adding each component together. Discrimination of the model was assessed using the concordance (*c*)-statistic. A *c*-statistic greater than 0.7 generally indicates a strong discriminative ability by the model.

VALIDATION PROCESS

We validated the prediction rule internally using the bootstrap method in the original derivation data set by resampling with 1000 iterations. Each bootstrap sample was the same size as the original derivation sample, but patients were drawn randomly with replacement from the sample.[11] For each iteration, Cox proportional hazards regression modeling was performed using risk score as the lone predictor of time to recurrence. Model summary statistics were averaged over the 1000 samples and compared with the original values. In addition, the number of times out of 1000 that the risk score was a significant predictor ($P<.05$) in the model was computed and expressed as a percentage.

Statistical calculations were performed with SAS statistical software (version 8; SAS Institute Inc, Cary, NC).

RESULTS

COHORT CHARACTERISTICS

A total of 1880 Olmsted County residents with a diagnostic code of interest during the study period were identified. Of these, 1758 (93.5%) agreed to participate in the REP. We were unable to locate the medical records of 4 persons. Of 1754 medical charts reviewed, 254 (14.5%) met the case definition of lower extremity cellulitis (**Figure 1**). To compare only patients with an initial episode of lower extremity cellulitis, 45 patients (17.7%) with a history of cellulitis that affected the ipsilateral lower

Table 1. Comparison of Clinical Characteristics of the 2 Study Cohorts With Lower Extremity Cellulitis (cont)*

Variable	No Recurrence (n = 174)	Recurrence (n = 35)	*P* Value†	Univariate HR (95% CI)‡
Anatomic site			•	
Foot	76 (44)	5 (14)		1 [Reference]
Tibial area	75 (43)	29 (83)		5.46 (2.11-14.1)§
Femoral area	23 (13)	1 (3)		0.63 (0.07-5.42)
Side: right or left			•	
Left	89 (51)	18 (51)		1.12 (0.58-2.17)
Right/both	85 (49)	17 (49)		1 [Reference]
Presenting site of care#			•	
Urgent care	58 (34)	9 (27)		1 [Reference]
Emergency department	53 (31)	13 (39)		1.49 (0.64-3.48)
Outpatient medical clinic	60 (35)	11 (33)		1.17 (0.48-2.82)
Antibacterial therapy: IV antibiotic**			.22	
None	111 (65)	19 (54)		1 [Reference]
Any	59 (35)	16 (46)		1.54 (0.79-3.00)
Third-generation cephalosporin	17 (11)	2 (6)		0.34 (0.08-1.54)
Cefazolin	32 (20)	12 (36)		1 [Reference]
Antibacterial therapy: oral antibiotic††			•	
Cephalexin hydrochloride	117 (69)	20 (57)		0.53 (0.23-1.21)
Other β-lactam antibiotic	31 (18)	7 (20)		0.69 (0.25-1.89)
Other antibiotic	22 (13)	8 (23)		1 [Reference]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; DVT, deep venous thrombosis; Fx: fracture; HR, hazards ratio; IV, intravenous; ND, no test for difference was performed; WBC, peripheral white blood cell count. Ellipses indicate that no test for difference was performed.

*Mean ± SD reported for continuous variables and number (percentage) for categorical variables.

†*P* value for *t* test/rank sum test displayed for continuous variables, and χ^2 test for association (or Fisher exact test when the expected cell frequency is <5) for categorical variables; "•" indicates that no test for difference was performed.

‡Hazard ratio (95% CI) determined from univariate proportional hazards regression models; "∟" represents a model failing to converge and produce parameter estimates, likely owing to small counts in the predictor variable.

§Highly significant ($P \leq .01$).

‖Significant ($.01 < P \leq .05$).

¶Borderline ($.05 < P \leq .10$).

#Five patients were not included in the regression model because they had been seen in a nursing home (n = 3) or another site of care (n = 2).

**Sixteen patients were not included in the regression model because either data were missing (n = 4) or they had received other types of antibiotics (n = 12).

††Four patients were not included in the regression model because either data were missing (n = 1) or they had not received an oral agent (n = 3).

Table 2. Results From Multivariate Analysis of Purported Risk Factors of Recurrent Lower Extremity Cellulitis

Covariate	HR (95% CI)	*P* Value
Anatomic site: tibial area	5.02 (2.03-12.42)	.001
History of cancer	3.87 (1.74-8.59)	.001
Ipsilateral dermatitis	2.99 (1.49-5.99)	.002

Abbreviations: CI, confidence interval; HR, hazard ratio.

extremity were excluded from analysis. **Table 1** summarizes the demographic characteristics of the remaining 209 patients. Thirty-five (16.7%) of them had experienced a recurrent episode of cellulitis at the same anatomic site of a lower extremity within 2 years.

A random 5% sample of the 1754 medical charts reviewed by the principal investigator (D.R.M.) was reviewed in a blinded fashion by senior investigators (L.M.B. and E.F.B.). Between investigators, there was 100% agreement on classification of cases based on the case definition.

UNIVARIATE ANALYSIS

Thirty-five (16.7%) of 209 patients experienced a recurrence of cellulitis at the same anatomic site within 2 years. Table 1 lists the results of univariate analysis of clinical characteristics and comorbid conditions of patients with recurrence of lower extremity cellulitis or vs those no with recurrence during the study period. The following variables were not listed in Table 1 owing to a very low frequency (n≤3) among the 2 patient groups: suppressive antibiotic use before or after the cellulitis episode; shock, nosocomial infection, or need for surgical debridement; early (≤72 hours) or late mortality (3-28 days); results of microbiologic cultures of specimens from toe web spaces, nares, and other anatomic sites; serologic examination for antideoxyribonuclease antibody and antistreptolysin O antibodies; corticosteroid use (≥20 mg prednisone per day); immunocompromised host status; end-stage renal disease; and end-stage liver disease.

MULTIVARIATE ANALYSIS

The results of multivariate analysis of risk factors for recurrence of lower extremity cellulitis are illustrated in **Table 2**. The final model predicting time until cellulitis recurrence consisted of 3 covariates: incident event occurring in the tibial area, history of cancer, and dermatitis. The *c*-statistic for the model was 0.77, indicating that the model performed well in predicting recurrence. The strongest independent predictor of 2-year

Table 3. Results From Predictive Model of Risk for Recurrence of Lower Extremity Cellulitis

Score*	Predicted Probability of Recurrence at Each Time Point, % (95% CI)			
	3 mo	6 mo	1 y	2 y
0	1.2 (0.2-2.3)	2.0 (0.4-3.5)	3.5 (1.0-5.9)	5.0 (1.6-8.2)
1	4.5 (1.6-7.2)	7.2 (3.5-10.8)	12.4 (7.3-17.3)	17.3 (11.1-23.0)
2	15.7 (6.4-24.1)	24.4 (12.8-34.4)	39.0 (24.5-50.8)	50.6 (34.2-63.0)
3	47.2 (10.4-68.8)	64.6 (22.2-83.9)	84.1 (39.7-95.8)	92.8 (51.9-98.9)

Abbreviation: CI, confidence interval.
*Sum of individual risk factor points (1 point each for tibial area involvement, history of malignancy, and presence of dermatitis at initial evaluation).

recurrence was the anatomic site: patients with tibial area cellulitis were 5 times more likely to experience recurrence than those with cellulitis in the foot or femoral region (HR, 5.02 [95% CI, 2.03-12.42], $P=.001$). Similarly, patients with a history of cancer vs those without had 4-fold elevated risk of recurrence (HR, 3.87 [95% CI, 1.74-8.59], $P=.001$). Furthermore, dermatitis affecting the ipsilateral lower extremity at the initial episode of cellulitis was predictive of recurrence, increasing the likelihood 3-fold (HR, 2.99 [95% CI, 1.49-5.99], $P=.002$).

PREDICTIVE MODELING

To construct a predictive model, a score using the 3 independent risk factors identified from multivariate analysis was developed and used to predict a subject's likelihood of recurrence at various time points within 2 years. Because each predictor had a regression coefficient and *P* value of similar range, 1 equally weighted point was assigned for each factor present. Thus, patients with the presence of all 3 risk factors had the highest possible risk score of 3, whereas those without any had the lowest possible risk score of 0. The predictive model of recurrence, with 1 main effect for risk score, had discriminative accuracy (*c*-statistic=0.72) comparable with that from the multivariate model with 3 risk factors. From the model, the predicted likelihood of recurrence, along with 95% CIs, was calculated and used to convey the risk for each score within 4 time points: 3 months, 6 months, 1 year, and 2 years. Results for all 4 risk scores at each of the 4 time points are shown in **Table 3** and **Figure 2**. Based on the predictive model, the estimated probability of recurrence within 2 years was 5.0% (95% CI, 1.6%-8.2%), 17.3% (95% CI, 11.1%-23.0%), 50.6% (95% CI, 34.2%-63.0%), or 92.8% (95% CI, 51.9%-98.9%) for a score of 0, 1, 2, or 3, respectively. Bootstrap resampling validated the model results because risk score was shown to be a significant predictor in 98% of the 1000 iterations.

KAPLAN-MEIER ANALYSIS

Kaplan-Meier analysis was performed to further assess the association between the risk factors and risk score from the predictive model and the rate of recurrence-free survival over a 2-year period. **Figure 3** illustrates the Kaplan-Meier curve for survival based on the risk score, or the sum of the 3 predictors present at a patient's initial assessment. (Individual Kaplan-Meier curves for overall recurrence and for recurrence that is based on each risk factor are available from us.) Based on the log-rank test, recurrence-free survival over 2 years was significantly lower for subjects with tibial area cellulitis, those with a history of cancer, or those with dermatitis ($P\leq.002$ for each). Furthermore, higher risk score values corresponded with lower survival. In each pair-wise comparison, with the 1 exception of score 2 vs score 3 (in which the power to detect a difference was limited considerably by only 2 subjects with scores=3), the recurrence-free survival rate was significantly lower for the higher score ($P\leq.01$ for each).

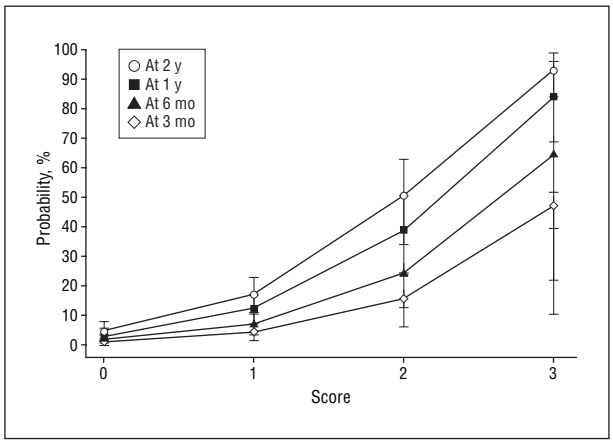

Figure 2. Association between the recurrent cellulitis score and probability of cellulitis recurrence. Prediction model score equals the sum of individual risk factor points (1 point each for tibial area involvement, history of malignancy, and dermatitis at initial evaluation). The bars represent 95% confidence intervals for predicted probabilities of recurrence up until time points 3, 6, 12, and 24 months.

COMMENT

Our findings suggest that a simple model that uses clinical data taken at the time of presentation of lower extremity cellulitis can predict the incidence of recurrent infection and provide a practicable prognostic decision aid. By using a population-based sample and excluding patients with previous bouts of cellulitis involving the same lower extremity, our survey provides the first analysis of risk factors for recurrence in patients with an initial episode of lower extremity cellulitis in a population-based sample. We found tibial area involvement with cellulitis, history of malignancy, and dermatitis of the ip-

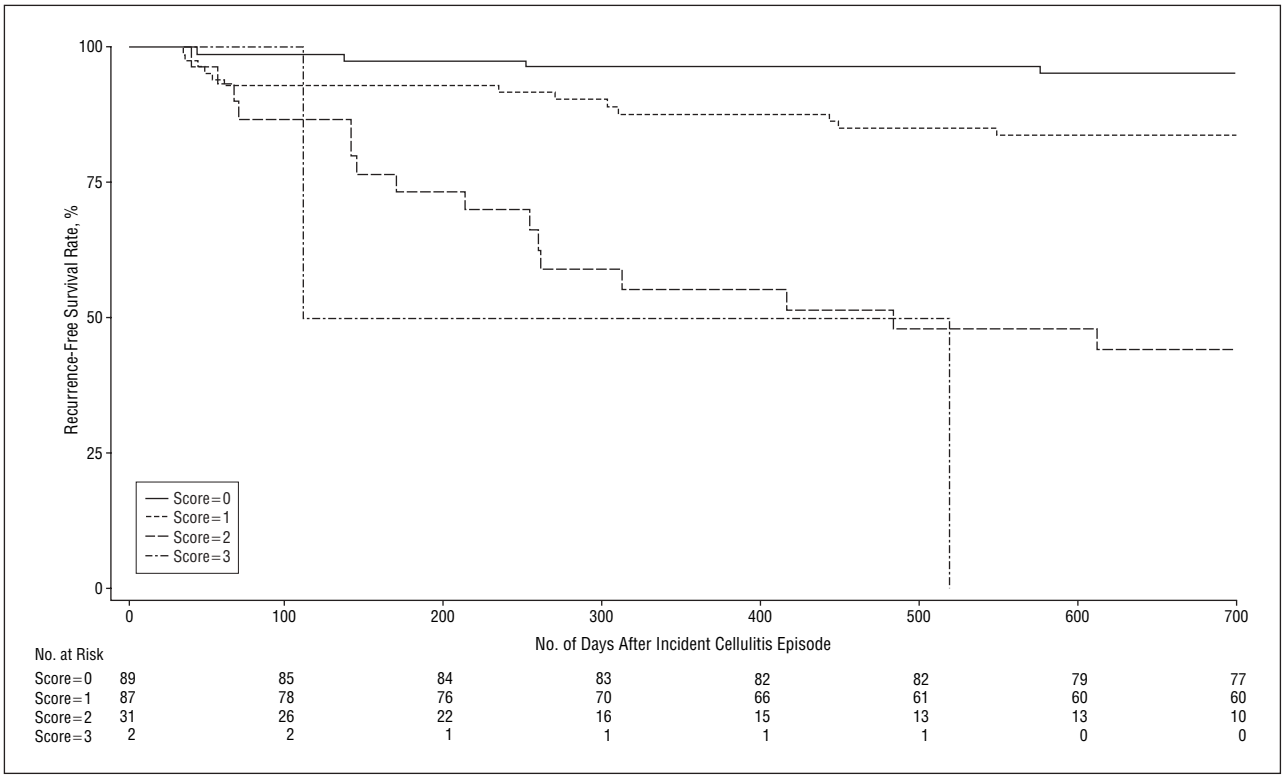

Figure 3. Kaplan-Meier curve of lower extremity cellulitis recurrence based on the predictive model score.

silateral limb to be risk factors for recurrence of lower extremity cellulitis on multivariate analysis.

Breeches in the integrity of skin have been suggested as portals of entry for bacteria to cause cellulitis,[8,12] and as a disruption in skin integrity, dermatitis is pathogenetically a plausible risk factor for recurrent infection. It is conceivable that disruption of skin integrity also could account for tibial area involvement of cellulitis as a risk factor for recurrent cellulitis. The frequency of minor trauma to the anterior tibial region, coupled with the presence of limited subcutaneous tissue and no musculature between skin and bone, creates a predisposing substrate for loss of skin integrity.

The association between invasive β-hemolytic streptococcal infection and malignancy may explain our finding of a nearly 4-fold increased risk of recurrence in patients with a prior diagnosis of cancer. β-Hemolytic streptococci are the most common causes of cellulitis,[13] and malignancy is a recognized risk factor for infection causing by these organisms.[14] Moreover, malignancy can be complicated by venous and lymphatic compromise, either directly owing to tumor effects or indirectly owing to radiotherapy as part of tumor treatment, and this vascular compromise predisposes to non–group A, β-hemolytic streptococcal infection.[15]

Our predictive model will assist physicians in identifying patients at highest risk for recurrence of lower extremity cellulitis. This model was developed by using variables identified with multivariate analysis and with population-based derivation cohort and internal validation by bootstrapping technique.

Anatomic site of lower extremity cellulitis and a history of malignancy are nonmodifiable risk factors. Nevertheless, these factors will help physicians caring for patients with lower extremity cellulitis identify those individuals at increased risk of recurrence. Successful treatment of the modifiable risk factor of dermatitis (and other pathogenetically plausible, modifiable risk factors of cellulitis including chronic edema, tinea pedis, and onychomycosis[1-3,8]) is expected to reduce the risk of a subsequent episode of lower extremity cellulitis.

To our knowledge, the only other published investigation of risk factors associated with recurrent lower extremity cellulitis was conducted by Bjornsdottir et al.[3] The patient cohort examined in that study differed from our patient population in several ways. First, only hospitalized patients were enrolled in that study,[3] so the cohort likely included a more ill population. Second, the case definition of cellulitis included the presence of fever, chills, or peripheral leukocytosis, which also likely selected for a sicker cohort. In that investigation,[3] previous leg (ipsilateral) surgery, other than saphenectomy, was statistically identified as a risk factor for recurrence.

A major strength of our study is that it is population based. The REP allowed us to identify lower extremity cellulitis cases among an entire population, thus avoiding potential selection bias that could be seen in the other studies[1,3] conducted among hospitalized patients. This allows a more accurate estimate of recurrence rate and risk factors of recurrence among a larger population of patients with lower extremity cellulitis seen by physicians in all settings.

Several limitations of our study deserve mention. By excluding patients with a history of cellulitis before study enrollment, we identified a relatively small sample (n=35) of patients with recurrence after an initial episode of lower

extremity cellulitis. This limited our ability to identify factors associated with risk of disease recurrence, and it is possible that with a larger sample size, factors such as leg swelling or onychomycosis that have been previously identified as risk factors for development of lower extremity cellulitis[1-3] (and were statistically significant in our univariate analysis) may have also been significant in multivariate analysis. Nevertheless, the aim of our study was not to derive an exploratory model to identify all possible risk factors but rather to derive a simple predictive model, which performed very well in identifying patients at high risk for recurrence.

This study relied on retrospective review of physician descriptions and diagnoses recorded in the medical records to determine agreement with a case definition, which placed limits on case ascertainment, inherent to all retrospective studies. In addition, Olmsted County has a predominately white racial composition, with a smaller racial and ethnic minority population and higher average educational levels than the United States as a whole,[4] which may limit generalization of these results to other populations. This prediction model needs external validation in other populations.

In summary, our population-based study of lower extremity cellulitis identified tibial area involvement, a history of malignancy, and the modifiable risk factor of dermatitis affecting the ipsilateral limb as risk factors for recurrence of disease. Based on our findings derived from a simple predictive model, patients at high risk for recurrent cellulitis can be identified. Further investigations should be undertaken to determine if treatment of modifiable risk factors reduces lower extremity cellulitis recurrence.

There was one additional published study (Mokni et al[16]) that was discovered after our manuscript was accepted for publication. In that case-control investigation, Mokni et al[16] demonstrated that disruption of the cutaneous barrier and leg edema were both independently associated with erysipelas of the leg in multivariable analysis. These findings are congruous with those cited in our study.

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REFERENCES

1. Dupuy A, Benchikhi H, Roujeau JC, et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. *BMJ*. 1999;318:1591-1594.
2. Roujeau JC, Sigurgeirsson B, Korting HC, Kerl H, Paul C. Chronic dermatomycoses of the foot as risk factors for acute bacterial cellulitis of the leg: a case-control study. *Dermatology*. 2004;209:301-307.
3. Bjornsdottir S, Gottfredsson M, Thorisdottir AS, et al. Risk factors for acute cellulitis of the lower limb: a prospective case-control study. *Clin Infect Dis*. 2005; 41:1416-1422.
4. Melton LJ III. History of the Rochester Epidemiology Project. *Mayo Clin Proc*. 1996;71:266-274.
5. World Health Organization. *International Classification of Diseases, Ninth Revision (ICD-9)*. Geneva, Switzerland: World Health Organization; 1977.
6. *Hospital Adaptation of the International Classification of Diseases, Adapted*. Ann Arbor, Mich: Commission on Professional and Hospital Activities; 1968.
7. Calandra GB, Norden C, Nelson JD, Mader JT; Infectious Diseases Society of America; US Food and Drug Administration. Evaluation of new anti-infective drugs for the treatment of selected infections of the skin and skin structure. *Clin Infect Dis*. 1992;15(suppl 1):S148-S154.
8. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis*. 2005;41: 1373-1406.
9. Efron B, Gong G. A leisurely look at the bootstrap, the jackknife, and cross-validation. *Am Stat*. 1983;37:36-48.
10. Fowler VG, Olsen MK, Corey GR, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. *Arch Intern Med*. 2003;163:2066-2072.
11. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361-387.
12. Swartz MN. Clinical practice. Cellulitis. *N Engl J Med*. 2004;350:904-912.
13. Hook EW III, Hooton TM, Horton CA, Coyle MB, Ramsey PG, Turck M. Microbiologic evaluation of cutaneous cellulitis in adults. *Arch Intern Med*. 1986; 146:295-297.
14. Ekelund K, Skinhoj P, Madsen J, Konradsen HB. Invasive group A, B, C and G streptococcal infections in Denmark 1999-2002: epidemiological and clinical aspects. *Clin Microbiol Infect*. 2005;11:569-576.
15. Baddour LM, Bisno AL. Non-group A beta-hemolytic streptococcal cellulitis: association with venous and lymphatic compromise. *Am J Med*. 1985;79:155-159.
16. Mokni M, Dupuy A, Denguezli M, et al. Risk factors for erysipelas of the leg in Tunisia: a multicenter case-control study. *Dermatology*. 2006;212:108-112.