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ORIGINAL RESEARCH

Differentiating Lower Extremity Necrotizing Soft Tissue Infection from Severe Cellulitis by Laboratory Parameters and Relevant History Points

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Background: Necrotizing soft tissue infection (NSTI) of the lower extremity (LE) is a rapidly progressing infection that requires early diagnosis and prompt treatment to decrease risks of loss of limb or life. Clinical presentation, particularly of early NSTI, can appear similar to severe cellulitis. The purpose of this study is to identify factors that are associated with NSTI rather than severe cellulitis to differentiate patients with similar clinical presentation.

Methods: This retrospective cohort design study compares patients finally diagnosed with LE NSTI versus those diagnosed with severe cellulitis. Cohorts were matched using the modified Laboratory Risk Indicator for Necrotizing Fasciitis (m-LRINEC) score in the setting of LE soft tissue infection. Laboratory values, vital signs, subjective symptoms, and social factors including substance abuse were recorded. Univariate and multivariate analyses were performed.

Results: Multivariate statistical analysis and clinical interpretation of data identified four factors more associated with a diagnosis of NSTI than severe cellulitis: elevated lactate, a patient-reported history of fever, male gender, and intravenous substance user.

Conclusion: In patients with lower extremity infections, the clinical presentation of NSTI and severe cellulitis may appear similar. In this retrospective cohort of patients matched with m-LRINEC scores, elevated lactate, subjective fever, male gender, and intravenous substance abuser were significantly associated with NSTI rather than severe cellulitis. Further studies of these factors in the clinical setting can help tailor the differential diagnosis in the care of patients with severe lower extremity infections. Matched with m-LRINEC scores, elevated lactate, subjective fever, male gender, and intravenous substance abuser were significantly associated with NSTI rather than severe cellulitis. Further studies of these factors in the clinical setting can help tailor the differential diagnosis in the care of patients with severe lower extremity infections.

Keywords: necrotizing soft tissue infection, cellulitis

Introduction

Necrotizing fasciitis (NF) is a severe, rapidly progressive disease that is characterized by the infection of subcutaneous tissue and fascia, resulting in extensive fascial necrosis.[1] Lower extremity (LE) NSTI is a limb- and life-threatening condition. Published mortality rates for LE NSTI range from ten to thirty percent, with reviews and meta-analyses publishing overall mortality rates of about 15–20%.[2–5] LE NSTI requires emergent surgical intervention including prompt debridement and intravenous

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antibiotics. Timely LE NSTI care is imperative; it has been shown that mortality rates increase steadily with each twenty-four hour period before the first operative debridement.[3] The first step in efficiently treating NSTI is diagnosing the condition.[6] Recognizing NSTI can be challenging, because early symptoms of NSTI, such as swelling, erythema, pain are non-specific and can occur with many different types of infections.[7] Since delay in NSTI diagnosis contributes to increased mortality, an accurate and efficient diagnosis of NSTI is imperative for successfully treating patients with NSTI.[8]

In 2004, a diagnostic scoring system called the Laboratory Risk Indicators for Necrotizing Fasciitis (LRINEC) score was created for this purpose.[9] The goal of the LRINEC score was to create a "simple and objective scoring system" based on routine laboratory values that could help distinguish NSTI from other soft tissue infections. However, in the ensuing validity studies, researchers found that the validity of the LRINEC had been overstated, and its sensitivity was 43.2–80.0% for a score of ≥6 and 28.6–68.4% for a score of ≥8 in different settings, countries or regions.[10–12] Some studies even demonstrated it to be non-specific.[12,13] Some authors have questioned if LRINEC scores added any diagnostic value.[12,14–17]

Wu et al developed a modified Laboratory Risk Indicator for Necrotizing Fasciitis (m-LRINEC) scoring system, which reported a better diagnostic value and published on June 2021.[18] The goal of this study is to compare a matched retrospective cohort of patients with LE NSTI to those with severe cellulitis. Within these two groups of similar m-LRINEC scores, this study identifies factors associated with NSTI rather than cellulitis to help in the clinical differentiation between these diagnoses that require different treatments.

Materials and Methods

Under the approval of institutional review board, a retrospective cohort study was conducted. The medical records of patients who met the inclusion criteria of surgically proven NF and who received management between January 2015 and January 2020 in two tertiary hospitals were reviewed. Selected comorbidities and initial laboratory values were extracted through medical chart review.

Sixty consecutive, surgically confirmed cases of LE NSTI were identified and assigned to the case group. A control population of 60 consecutive cases of LE severe cellulitis were also reviewed. The control population was matched to the NSTI cohort through average m-LRINEC

scores. Because the average m-LRINEC score for the NSTI group was expectedly elevated, eligibility for the control group included a m-LRINEC score of 8 or greater. The goal of this design was to focus on the cases where it is challenging to clinically differentiate between NSTI and cellulitis. For all included patients, variables collected for data analysis were grouped into one of three categories: laboratory values, vital signs at emergency department (ED) presentation, and qualitative data on symptoms and social factors.

Lab values collected for each patient included m-LRINEC score and its six components high-sensitivity C reactive protein (HCRP), white blood cell count, hemoglobin, sodium, creatinine, and blood glucose, erythrocyte sedimentation rate, lactate, and international normalized ratio. Vital signs at ED presentation that were collected for each patient include maximum temperature (Tmax), maximum heart rate (HRmax), maximum respiratory rate (RRmax), maximum systolic blood pressure (SBPmax), minimum systolic blood pressure (SBPmin), maximum diastolic blood pressure (DBPmax), minimum diastolic blood pressure (DBPmin), maximum mean arterial pressure (MAPmax), minimum mean arterial blood pressure (MAPmin), change in systolic blood pressure (dSBP), change in mean arterial pressure (dMAP), maximum pulse pressure (PPmax), and minimum pulse pressure (PPmin). Additional identifying information, including age and time to presentation, were also grouped into this category. The patient and infection characteristic variables recorded for each case include patient gender, laterality of injury (right or left), homelessness, patient provided history of recent intravenous substance use, subjective fever, and objective fever.

For our statistical analyses, all continuous variables were compared with Mann–Whitney U, whereas categorical variables were compared with chi-square test or Fisher exact test (for expected values less than 5). A binary logistic regression for continuous and categorical variables was also performed. Significance was set at p<0.05. Univariate and multivariate analysis was performed.

Results

In analysis of the quantitative date: lab results and vital signs, univariate and multivariate analyses were performed. Univariate analysis of lab values identified statistically significant differences in two variables – WBC and lactate (Table 1). WBC values were significantly higher in the cohort of patients with NSTI (21.2 ± 9.4) compared to the cohort with cellulitis (15.2 ± 6.3) (p=0.02). Lactate levels were significantly higher among NSTI patients (18.3 ± 10.5) than

Table 1 Laboratory Values from NF and Control Group are Compared Using a Mann–Whitney *U*-Test

Continue Variables	NF Group (n=60)		Control Group (n=60)		P-value
	(Mean±SD)	Range	(Mean±SD)	Range	
m-LRINEC score	25.1 ± 9.8	(10–50)	12 ± 6.9	(8–35)	–
Age	49.1 ± 13.2	(23–90)	46.2 ± 13.8	(21–88)	0.17
HCRP (mg/dL)	110.5 ± 76.3	(28–306)	65.8 ± 20.5	(15–104)	0.06
WBC (x10^4 /uL)	21.2 ± 9.4	(6.8–51)	15.2 ± 6.3	(3.7–25.6)	0.02*
Blood glucose(mg/dL)	214.8 ± 149.6	(83–968)	172.9 ± 122.7	(64–985)	0.59
Sodium (mEq/L)	134.5 ± 7.1	(115–152)	134.6 ± 5.6	(118–158)	0.44
Lactate (mg/dL)	18.3 ± 10.5	(12–109)	8.6 ± 7.1	(9–36)	< 0.01*
INR	1.3 ± 0.4	(0.7–3.6)	1.1 ± 0.2	(0.8–1.5)	0.19
ESR	53.1 ± 28.5	(14–109)	61.9 ± 28.6	(8–102)	0.84
Hemoglobin	12.2 ± 2.5	(4.8–16.6)	11.4 ± 2.8	(7.6–16.8)	0.63
Tmax	37.7 ± 0.9	(36.5–39.4)	37.5 ± 0.8	(36.2–39.7)	0.43
Time to presentation (days)	6.5 ± 4.2	(0–13)	5.2 ± 3.6	(0–16)	0.74

Note: *P < 0.05.
Abbreviations: HCRP, high sensitive C reactive protein; WBC, white blood cell count; INR, international normalized ratio; ESR, erythrocyte sedimentation rate; Tmax, maximal temperature at ED; SD, standard deviation.

cellulitis patients (8.6 ± 7.1) (p<0.01). Notably, other components of the m-LRINEC score, such as HCRP, hemoglobin, sodium, creatinine, and blood glucose were not different between the two groups. In the multivariate analysis of these laboratory variables, only elevated lactate remained statistically significant (OR = 3.87, p<0.01). Univariate analysis of vital signs data identified statistically significant, but clinically insignificant, differences in three variables – SBP max, dSBP and, PPmax (Table 2). In the multivariate analysis, no differences in vital signs were found to be statistically significant.

In the analysis of qualitative data, univariate analysis identified significant differences in four variables – homelessness, IV substance user, subjective fever, and gender (Table 3). Patients with NSTI were significantly more likely to be undomiciled (16.7%) than patients with cellulitis (3.3%) ($\chi2$ = 11.32, p<0.01). Additionally, patients in the NSTI cohort were more likely to abuse IV drugs (20.0%) than patients in the cellulitis cohort (5.0%) ($\chi2$ = 15.05, p<0.01). Patients with NSTI diagnosis were more likely to have self-reported a subjective fever (50.0%) than patients with cellulitis (26.7%) ($\chi2$ = 16.62, p<0.01). In the

Table 2 Vital Signs from NF and Control Group are Compared Using a Mann–Whitney *U*-Test

Continue Variables	NF Group (n=60)		Control Group (n=60)		P-value
	(Mean±SD)	Range	(Mean±SD)	Range	
HRmax	111.5 ± 19.6	(72–150)	103.5 ± 18.5	(66–140)	0.06
RRmax	23.0 ± 5.9	(10–39)	22.1 ± 12.8	(18–35)	0.25
SBPmax	130.2 ± 20.3	(104–198)	150.8 ± 12.5	(118–194)	0.02*
DBPmax	85.7 ± 14.4	(46–117)	84.4 ± 13.6	(54–113)	0.78
MAPmax	103.5 ± 14.9	(76–129)	107.0 ± 13.7	(81–136)	0.27
SBPmin	110.3 ± 17.1	(70–148)	112.5 ± 18.6	(64–152)	0.56
DBPmin	67.5 ± 12.3	(44–86)	65.8 ± 12.2	(36–94)	0.97
MAPmin	82.1 ± 13.5	(58–112)	82.5 ± 13.2	(56–110)	0.73
dSBP	26.8 ± 19.1	(0–75)	35.9 ± 14.5	(4–95)	0.04*
dMAP	21.4 ± 14.7	(0–69)	24.4 ± 11.2	(3–45)	0.22
PPmax	53.4 ± 19.2	(18–88)	63.7 ± 14.6	(40–86)	< 0.01*
PPmin	43.8 ± 11.2	(21–74)	44.6 ± 14.3	(17–69)	0.83

Note: *P < 0.05.
Abbreviations: HRmax, maximum heart rate in ED; RRmax, maximum respiratory rate in ED; SBPmax, maximum systolic blood pressure in ED; DBPmax, maximum diastolic blood pressure in ED; MAPmax, maximum mean arterial pressure in ED; SBPmin, minimum systolic blood pressure in ED; DBPmin, minimum diastolic blood pressure in ED; MAPmin, minimum mean arterial pressure in ED; dSBP, delta systolic pressure; dMAP, delta mean arterial pressure; PPmax, maximum pulse pressure; PPmin, minimum pulse pressure.

Table 3 Categorical Variables from NF and Control Group are Compared Using a Chi-Squared Test

Categorical Variables	NF Group (n=60)		Control Group (n=60)			p-value
	(n)	%	(n)	%	χ2	
Gender					6.65	0.01
Male	42	70.0%	37	61.7%		
Female	18	30.0%	23	38.3%		
Laterality					0.06	0.81
Left	25	41.7%	24	40.0%		
Right	35	58.3%	36	60.0%		
Homeless					11.32	< 0.01
Yes	10	16.7%	2	3.3%		
No	50	83.3%	58	96.7%		
IV substance use					15.05	< 0.01
Yes	12	20.0%	3	5.0%		
No	48	80.0%	57	95.0%		
Subjective fever					16.62	< 0.01
Yes	30	50.0%	16	26.7%		
No	30	50.0%	44	73.3%		
Objective fever					3.44	0.07
Yes	23	38.3%	26	43.3%		
No	37	61.7%	34	56.7%		

Note: Patients with an "objective fever" have a temperature > 37.5 degrees Celsius.

multivariate analysis, subjective fever (OR = 13.74, p=0.003), IV substance use (OR = 13.98, p=0.001), and gender (OR = 15.47, p=0.016) all remained statistically significant (Table 4).

Discussion

Early diagnosis and surgical debridement of LE NSTI is a critical part of treatment in patients with this limb and life-threatening condition. It is often challenging to definitively diagnose NSTI when the clinical picture is similar to cellulitis. By creating a matched group of control patients with LE cellulitis with, by design, similar m-LRINEC scores, this research identifies other observable clinical factors associated with NSTI rather than cellulitis. Our results indicate that WBC and lactate levels differ between patients with NSTI and those with serious cellulitis and abscess. While the NSTI group and control group were initially matched through average m-LRINEC scores, WBC - a component of m-LRINEC - still differed significantly between the two groups. Some published studies have linked elevated lactate to NSTI diagnosis, and the clinical use of monitoring lactate levels in critically ill patients is common.[19] Wu et al proposed other MLRINEC score which assigned highest score in lactate >18 mg/dL (OR 4.49, 95% CI 2.66–12.5.4).[20] Daniels et al also raised a lactate-based scoring system due to the lactate values were statistically

Table 4 Binary Logistic Regression Displays All Significant Statistically Variables

Factor	B	S.E	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Gender	2.71	1.15	5.69	1.00	0.016	15.47	1.63	98.95
Subjective fever	2.61	0.87	9.12	1.00	0.003	13.74	0.014	0.478
IV substance user	2.63	0.82	10.38	1.00	0.001	13.98	2.95	58.41
Lactate	1.54	0.58	7.34	1.00	0.006	4.970	1.52	13.85
Constant	−2.28	1.27	3.22	1.00	0.078	0.152	–	–

significant higher in necrotizing infection group 4.1 vs 2.0 mmol/l (p < 0.001).[21] Their finding was similar with our study in the role of elevated lactate. Lactate is a quick, reliable predictor of morbidity and mortality. Additionally, lactate monitoring has been used successfully in risk-stratification for critically ill patients.[19,22] Specifically in regards to NSTI infections, lactate monitoring has been used in multiple studies as a predictor of NSTI mortality rates.[23,24] Although patients with cellulitis may appear clinically similar at presentation to those with NSTI, the association of higher WBC and higher lactate levels indicate a higher risk to limb and life in patients with LE NSTI. Our results did not find a statistically or clinically meaningful difference in vital signs on initial presentation between the cellulitis group and the NSTI group. Both groups, on average, were tachycardic on hospital presentation. The cause of tachycardia is likely multifactorial. Although it was not clinically or statistically different between the two groups, it is important to record in all patients who present with serious LE infection. In the literature, tachycardia is described as a symptom of NSTI and, in some studies, it has been linked to increased morality rate in patients being treated for NSTI.[25,26]

Although SBP max, dSBP, PPmax were found to be statistically significant in univariate analysis, the differences were not found to be statistically significant in multivariate analysis. Moreover, we do not find the differences in the values to be clinically significant. Analysis of our data indicates that social factors, including housing status and IV substance abuse, are more associated with LE NSTI versus cellulitis of the LE. A strong association between homelessness and LE NSTI was found in both univariate and multivariate analysis. There is limited data in the current literature linking homelessness to NSTI infection. There are epidemiological studies describing outbreaks of *Group A Streptococcal (GAS)* infection – a cause of both NSTI and cellulitis among a homeless population with incidence of up to 53 times the domiciled population.[27,28] However, our study is the first to report a statistically significant association between IV substance use and diagnoses of NSTI as opposed to other serious LE soft tissue infections. Though both study populations contained a majority of male patients, gender showed statistical significance in both univariate and multivariate analysis. The group of patients with NSTI was overwhelmingly male compared to the group of patients with cellulitis. This finding is consistent with prior studies reporting higher rates of both cellulitis and NSTI in male patients.[29–31] However, the

clinical significance of this statistical finding is limited, because both groups with soft tissue LE infections show a significant association with male gender.

An additional statistically significant variable found in the analysis of our data is a history of subjective fever. Although subjective fever was more associated with NSTI versus cellulitis, measured temperature and the presence of an objective fever in the emergency department were not significantly associated with one diagnostic group on either univariate or multivariate analysis. Subjective reports of symptoms have been linked to NSTI diagnosis previously, but this is the first association between LE NSTI and subjective fever. Subjectively reported fever may indicate a history of fever since the condition developing from the beginning. Objectively measured fever may be affected by anti-pyretic medication and self-regulation. Subjective fever may reflect more exactly of clinical condition. There are several weaknesses of this study. Firstly, this is a retrospective study that may not be generalizable to other patient populations. In our patient population, LE NSTI seems to disproportionately affect an under researched and under-served population of individuals with a high rate of IV substance abuse and homelessness. Pain out of proportion was mentioned in improving a clinical score for NSTI,[32] however, level of pain could not be replicable in our retrospective setting. Future studies to early diagnosis of NSTI versus cellulitis should be prospective and, instead of using m-LRINEC scores to match a cohort, could identify patients on clinical presentation where the diagnosis of NSTI versus cellulitis is in question.

Conclusions

In conclusion, swift and reliable differentiation of LE NSTI from severe cellulitis is of vital clinical importance. This may lead to a limb or life-saving surgical intervention. It is often clinically challenging to accurately differentiate between these illnesses. In cases where the clinical and laboratory evaluation may not give a clear diagnosis, an elevated WBC, lactate, IV substance abuse, and subjective fever should lead clinicians to an increased consideration of LE NSTI for their diagnosis.

Abbreviations

CI, confidence interval; HCRP, high sensitive C-reactive protein; ED, emergency department; Hb, hemoglobin; LE, low extremity; LRINEC, laboratory risk indicator for necrotizing fasciitis; NSTI, necrotizing soft tissue infection; SD, standard deviation; WBC, white blood cell; INR, international normalized ratio; ESR, erythrocyte sedimentation rate.

Data Sharing Statement

All the data will be available upon motivated request to the corresponding author of the present paper.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and the institutional review board of Chiayi Chang Gung Memorial Hospital approved this retrospective study (100-4178B) and (201900447B0C601). Consent to participate was not required. The IRB confirm that the data was anonymized or maintained with confidentiality.

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Disclosure

The authors declare that they have no competing interests.

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