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RESEARCH ARTICLE

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Severe skin and soft tissue infection in cohort patients admitted in a teaching hospital in Belgium: identification of risk factors for surgery

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ABSTRACT

Background: Necrotizing soft tissue infections (NSTIs) are associated with significant mortality if not promptly diagnosed and surgically treated.

Aim: This study aims to compare patients with severe skin and soft tissue infection treated with or without a surgical intervention and to identify risk factors that can predict the need for early surgery.

Methods: Demographics, clinical, laboratory, Risk Indicator for Necrotizing Fasciitis (LRINEC) and imaging results were retrospectively collected.

Results: There were 91 non-NSTI (group 1), 26 NSTI who were operated (group 2) and eight suspected NSTI who were not operated (group 3). In the multivariate analysis, skin necrosis, tachycardia, CRP value and hyperglycemia were predictive for surgery. A performance analysis revealed AUC of 0.65 (95%CI: 0.52–0.78) as to the LRINEC score for the use of surgery. The AUC for a predictive model associating four variables (heart rate, skin necrosis, CRP and glycemia at admission) was 0.71 (95%CI: 0.59–0.84). In terms of outcome, the median length of stay (LOS) was statistically higher in group 2 vs. group 1 (seven days (5–15) vs. 34 days (20–42), $p < .001$) and in group 2 vs. group 3 (34 days (20–42) vs. 14 days (11–19), $p = .005$). The overall in-hospital mortality at 30 days was 3.2% and did not statistically differ between the three groups.

Conclusions: Although the LRINEC score performed well in predicting surgery, the AUC of a model combining four predictive variables (glycemia, skin necrosis, CRP and heart rate) was superior. Further research is needed to validate this model.

KEYWORDS
Skin infection
LRINEC
modified LRINEC
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Introduction

Skin and soft tissue infections (SSTIs) account for more than 14 million physician office visits each year in the United States and emergency department visits and hospitalizations [1]. SSTI results from microbial invasion of the skin and its supporting structures. Management is determined by the severity and location of the infection and by patient comorbidities. Infections can be classified as simple (uncomplicated) or complicated (necrotizing or non-necrotizing), or as suppurative or non-suppurative [2]. Necrotizing soft tissue infections (NSTIs) are rare, aggressive soft tissue infections with significant morbidity and mortality if not diagnosed promptly and rapidly treated by surgery [2–5]. NSTI remains challenging to diagnose given their rarity and wide clinical spectrum range, resulting in a lack of specific diagnostic criteria [2,6–8]. Multiple predictive models and scores have been proposed to help distinguish NSTI from non-necrotizing soft tissue infections [7–10]. Although initially promising, these models and scores were not well validated in subsequent studies [2,11–13]. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was published in 2004 and used the total white-cell count, hemoglobin, sodium, glucose, creatinine and C-reactive protein (CRP) [9]. LRINEC's score specificity is greatest for advanced disease. This notion is supported by a recent study in which 70% of patients admitted to the intensive care unit with necrotizing fasciitis (NF) had an LRINEC score of greater than 6 and the mortality was 29.3% [14]. Subsequent studies have demonstrated the tool's limited sensitivity when scores are less than 6 and therefore it should not be used to rule out a NSTI [13,15,16]. Borschitz et al. [10] proposed a modified LRINEC score by replacing sodium and glucose levels with erythrocyte count and fibrinogen level. They also add clinical variables such as pain, fever, tachycardia and signs of acute kidney injury. In doing so, they were able to increase the positive and negative predictive values but this modified LRINEC score have not been validated by other studies. Moreover, some data were lacking such as time to surgery and overall mortality which is very important to narrow the delay between diagnosis and surgery. In fact, mortality associated with delay in surgical debridement is high, so recent guidelines recommend early surgical debridement (within 12–24 h of diagnosis) [17,18]. However, high index suspicion based on clinical symptoms, laboratory and imaging such as magnetic resonance imaging (MRI) remains essential to avoid delayed surgery. Identifying risk factors or/and patients at increased risk to develop severe SSTI requiring surgery is of great importance [2,7,8,18].

This study aims to compare patients with severe skin and soft tissue infection (sSSTI) whose treatment involved or not a surgical intervention and to identify risk factors that can predict the need for early surgery.

Methods

Setting and patients

This retrospective study was performed in a teaching hospital of 973 beds, Cliniques Universitaires Saint-Luc (CUSL) in Brussels, Belgium. The institutional ethical board approved the study (N°CEHF: 2019/04Jul/299). We retrospectively included patients with sSSTI between January 2015 and December 2019. sSSTI here refers to complicated soft tissue infection (necrotizing or non-necrotizing) requiring hospitalization (patients with systemic signs such as fever, tachypnea, abnormal white cell count or immunocompromised patients). We divided patients into three groups. The first group (group 1) included patients with non-NSTI referred to as severe soft tissue infection. The second group (group 2) included patients with high suspicion of NSTI who were operated on based on clinical, laboratory and imaging (MRI) findings. The results of tissue samples collected during surgery showed findings including the obliteration of soft tissue planes, dish water fluid, subcutaneous tissue necrosis, fascia and/or muscle requiring debridement for source control on a surgical report or/and histology. The third group (group 3) included patients with suspicion of NSTI based on clinical, labs and imaging (MRI) findings but who were not operated on as per the decision of our multidisciplinary team. Of note, in our hospital, all cases with high suspicion of NSTI are discussed by a multidisciplinary team involving an experienced infectiologist, a plastic or orthopedic surgeon, and a radiologist with the decision to perform early surgery (within 24 h) being taken on a case by case basis.

Data collection

Demographics and clinical characteristics, laboratory parameters and imaging (MRI) results were collected. Demographics included age, sex and ethnicity. Clinical characteristics included symptoms at admission (fever, redness, pain, skin necrosis, skin discoloration (violaceous or purplish), hypoesthesia, vital signs, localization, etc.), comorbidities (diabetes, hypertension, cancer),

immunosuppression (HIV, chronic corticosteroids use, chemotherapy, immunosuppression induced by various drugs), cardiovascular diseases, arteriopathy, chronic lymphoedema, chronic kidney diseases, cirrhosis, alcoholism, illicit drug abuse, etc.

Skin necrosis was defined as dead skin tissue, usually black.

Laboratory parameters included CRP, complete blood count (neutrophils count, lymphocyte, neutrophil to lymphocyte ratio (NLR)), natremia, urea, creatinine, lactate dehydrogenase (LDH), glycemia, lactate and creatine phosphokinase (CK). Pain definition was as following: severe, medium and none. Laboratory Risk Indicator for Necrotizing Fasciitis and modified LRINEC scores were calculated. The imaging technique used was mainly MRI and was performed in those cases with a high index of suspicion of NSTI to explore the presence of gas, fluid, collection, abscess, tissue necrosis, fascia involvement and to guide surgery if necessary. Nevertheless, echography and CT-scan were also performed during the night in some cases.

MRI tissue necrosis was defined as avascular tissue around the deep fascia (fascia necrosis).

Three outcomes were recorded: the overall 30-day in-hospital mortality, the number of amputations, and the length of stay (LOS).

Statistical analysis

All analyses were conducted using SPSS 27 software (IBM SPSS Statistics for Windows, Version 27.0, IBM Corp., Armonk, NY). Continuous variables were expressed as mean and standard deviation or median and interquartile range and were compared using an unpaired *t*-test (or Mann–Whitney–Wilcoxon's test when appropriate). Categorical variables were expressed as counts and percentages and analyzed using the Chi-squared test or Fisher's exact test. In order to find factors associated with surgery, odds ratio and adjusted odds ratio were calculated using univariate and multivariate logistic regression analysis. Variable selection was performed with a method of backward elimination based on the likelihood ratio, using a criterion of *p* value less than .20 for retention in the model. Receiver-operating characteristic (ROC) curves were generated to assess the performance of significant variables in discriminating the use of surgery. Areas under the receiver-operating curve (AUROC) were compared using the method of Hanley and McNeil. All tests were two-sided, with .05 as the significance threshold.

Results

In total, 125 patients were included in the study. There were 91 non-NSTI (group 1), 26 NSTI who were operated (group 2) and eight suspected NSTI who were not operated (group 3). Demographics and clinical characteristics are summarized in Tables 1 and 2. The mean age for each of the three groups (±standard deviation) was 65 ± 17.62 ± 12.55 ± 23 and there were 47%, 54% and 62% of men in groups 1, 2 and 3, respectively. Comorbidities were similar between all groups.

Imaging

For the 91 non-NSTI, 87 imaging modalities were performed (42 MRI, 10 CT-scan and 35 echography). Their findings were not compatible with NSTI; only in two patients, MRI described minor signs of necrosis. For 26 NSTI who were operated on (group 2) and eight suspected NSTI who were not operated on, MRI was performed in all patients showing findings compatible with NF including thickening of the deep fasciae, with high signal on T2 images and contrast-enhanced T1 images, fascia necrosis. Necrosis was described in operated NSTI in 12 out of 26 patients (46%) and in non-operated NSTI in five out of eight patients (62%).

Histology

Frozen biopsy was obtained for 23/26 NSTI who were operated on. All confirm findings compatible with NF, including necrosis of superficial fascia, polymorphonuclear infiltration of the deep dermis and fascia, fibrinous thrombi of arteries and veins passing through the fascia, angiitis with fibrinoid necrosis of vessel walls and microorganisms within the destroyed fascia and dermis.

Microbiology

Globally, *Staphylococcus aureus* represented 23%, *group A Streptococcus* (GAS) 13%, other *Streptococcus* species 13%, *Escherichia coli* 13%, Enterobacteriaceae other than *Escherichia coli* 10%, others gram-negative 13% and anaerobies 13%. Microbiological findings in the different groups are presented in Table 3.

Comparison of group 1 (non-NSTI) with group 2 (NSTI who were operated)

When comparing group 1 with group 2, group 2 had significantly more skin necrosis, violaceous or purplish

Table 1. Comparison between patients with non-NSTI (group 1) and NSTI with surgical management (group 2).

Variables	Non-NSTI ($n = 91$)	NSTI with surgery ($n = 26$)	p Value
Demographics			
Age	65 ± 17	62 ± 12	.58
Men	43 (47)	14 (54)	.55
Weight (kg)	81 ± 23	88 ± 19	.17
Height (cm)	171 ± 12	170 ± 10	.62
Infection characteristics			
Polymicrobial	13 (14)	7 (28)	.11
Bacteremia	4 (4)	5 (19)	.01
Microbiological documentation	37 (41)	23 (88)	<.001
Necrosis on MRI	2 (2)	12 (46)	<.001
LRINEC score	3.9 ± 2.6	6.2 ± 2.7	<.001
Modified LRINEC score	7.1 ± 3.6	10.6 ± 4.3	<.001
Type of surgery			
Debridement	5 (5)	21 (81)	<.001
Abscess drainage	7 (7)	2 (8)	
Curettage/osteitis	2 (2)	0	
Fasciotomy	1 (1)	0	
Amputation	1 (1)	2 (8)	
Comorbidities			
Cancer	15 (17)	2 (8)	.25
Diabetes	17 (19)	10 (38)	.03
Cardiac insufficiency	18 (20)	7 (27)	.43
Hypertension	48 (53)	13 (50)	.8
Peripheral arteriopathy	24 (26)	5 (19)	.46
Chronic liver disease	2 (2)	0	.45
Hemodialysis	1 (1)	0	.59
Chronic uptake of corticosteroid	13 (14)	4 (15)	.89
Chemotherapy	5 (5)	1 (4)	.74
Immunosuppression	12 (13)	6 (23)	.22
Alcohol			
Current alcohol abuse	7 (7)	4 (15)	.5
Lymphoedema	5 (5)	1 (4)	.74
Clinical characteristics			
Fever	38.3 ± 0.6	37.4 ± 1.4	.75
Pain	80 (88)	26 (100)	.07
Redness	88 (97)	24 (92)	.33
Violaceous or purplish	3 (3)	5 (19)	.01
Skin necrosis	4 (4)	7 (27)	.001
Hypoesthesia	3 (3)	0	.34
Shock	3 (3)	9 (35)	<.001
Heart rate	88 ± 18	102 ± 17	<.001
Systolic blood pressure	132 ± 22	116 ± 28	.03
Diastolic blood pressure	73 ± 15	65 ± 15	.03
Laboratory values			
C-reactive protein (mg/dL)	143 ± 107	231 ± 137	<.001
Hemoglobin (g/dL)	12 ± 1.9	12 ± 2.3	.63
Neutrophil count (cells/mm^3)	9131 ± 4186	1206 ± 6057	.003
NLR	12.6 ± 16	13.9 ± 10	.62
LDH (UI/L)	231 ± 80	256 ± 90	.18
Glycemia at admission (mg/dL)	126 ± 51	197 ± 127	<.001
Urea (mg/dL)	56 ± 49	68 ± 46	.2
Creatine (mg/dL)	1.36 ± 1.32	1.7 ± 1.2	.2
Natremia (mM)	137 ± 4	135 ± 4.7	.011
Creatine Phosphokinase (UI/L)	71 [45–123]	119 [38–450]	.25
Fibrinogen (mg/dL)	648 ± 238	612 ± 217	.99
Outcome			
Mortality at 30 days	3 (3)	1 (4)	.62
Need for amputation	1 (1)	2 (8)	.054
Hospital length of stay	7 [5–15]	34 [20–42]	<.001

MRI: magnetic resonance imaging; NLR: neutrophil to lymphocyte ratio; IQR: interquartile ratio.
All variables are mean ± standard deviation, or median [IQR], or count and percentage of the group.

skin discoloration, tachycardia, hypotension compatible with signs of shock. High CRP, neutrophil count, urea levels, lactate levels, CK and hyponatremia were significantly more common in group 2. We also found that bacteremia, microbiological identification of a pathogen, necrosis description on MRI were significantly associated with group 2; LRINEC score (6.2 ± 2.7 vs. 3.9 ± 2.6, $p < .001$) and modified LRINEC score (10.6 ± 4.3 vs. 7.1 ± 3.6, $p < .001$) scores were higher in group 2 compared to group 1. In terms of outcomes, the median LOS (seven days (5–15) vs. 34 days (20–42), $p < .001$) was statistically higher in group 2 vs. group 1. The overall in-hospital mortality at 30 days was 3.2% but did not differ between both

Table 2. Comparison between patients with NSTI for whom surgery was performed (group 2) or not (group 3).

Variables	Surgery group ($n = 26$)	No surgery group ($n = 8$)	p Value
Demographics			
Age	62 ± 12	55 ± 23	.33
Men	14 (54)	5 (62)	.66
Weight	86 ± 12	87 ± 41	.88
Height	170 ± 10	167 ± 14	.57
Infection characteristics			
Diagnosis category			
Cellulitis	1 (4)	2 (25)	.001
Dermohypodermitis	1 (4)	5 (62)	
Necrotizing fasciitis	12 (46)	1 (12)	
Abscess	3 (12)	0	
Necrotizing myositis	2 (8)	0	
Gas gangrene	7 (26)	0	
Polymicrobial	7 (28)	0	.15
Bacteremia	5 (19)	0	.33
Microbiological documentation	24 (92)	2 (25)	.001
Localization			
Member	21 (80)	7 (88)	.77
Perineal	2 (8)	0	
Cervico-thoracic	1 (4)	0	
Mixed localization	2 (8)	1 (12)	
Necrosis at MRI	12 (46)	5 (62)	.42
LRINEC score	7 [4.5–8]	3 [0.25–4.50]	.23
Modified LRINEC score	12 [8–14]	9 [5–12]	.46
Comorbidities			
Cancer	2 (8)	1 (12)	.99
Diabetes	10 (38)	2 (25)	.48
Cardiac insufficiency	7 (27)	1 (12)	.64
Hypertension	13 (50)	3 (37)	.69
Peripheral arteriopathy	5 (19)	2 (25)	.99
Chronic corticosteroid use	4 (15)	2 (25)	.61
Chemotherapy	1 (4)	1 (12)	.42
Immunosuppression	6 (23)	2 (25)	.99
Alcohol abuse	4 (15)	1 (12)	.83
Lymphoedema	1 (4)	2 (25)	.13
Clinical characteristics			
Fever	37.4 ± 1.4	38.3 ± 1	.08
Pain	26 (100)	2 (25)	.04
Redness	24 (92)	8 (100)	.42
Violaceous or purplish	5 (19)	0	.31
Skin necrosis	7 (27)	1 (12)	.64
Hypoesthesia	0	1 (12)	.23
Shock	9 (35)	0	.07
Heart rate	102 ± 17	99 ± 21	.65
Systolic blood pressure	116 ± 28	114 ± 13	.7
Diastolic blood pressure	65 ± 15	70 ± 14	.51
Laboratory values			
CRP (mg/dL)	231 ± 137	171 ± 65	.24
Hemoglobin (g/dL)	12 ± 2.3	11.7 ± 1.16	.64
Neutrophils (cells/mm^3)	1206 ± 6057	11,045 ± 3861	.61
NLR	13.9 ± 10	14 ± 10	.93
LDH (UI/L)	256 ± 90	218 ± 68	.28
Glycemia (mg/dL)	197 ± 127	101 ± 25	.002
Urea (mg/dL)	68 ± 46	39 ± 48	.007
Creatine (mg/dL)	1.7 ± 1.2	0.56 ± 0.58	.15
Natremia (mM)	135 ± 4.7	136 ± 2.6	.36
Creatine phosphokinase (UI/L)	119 [38–450]	70 [53–119]	.62
Fibrinogen (mg/dL)	612 ± 217	659 ± 223	.42
Outcome			
Mortality at 30 day	1 (4)	0	.99
Need for amputation	2 (8)	0	.99
Hospital length of stay	34 [20–42]	14 [11–19]	.005

MRI: magnetic resonance imaging; NLR: neutrophil to lymphocyte ratio; IQR: interquartile ratio.
All variables are mean ± standard deviation, or median [IQR] or count (percentage of the group).

groups. The number of amputations tended to be higher in group 2 than group 1 (2 vs. 1, $p = .054$), but the number was too low to draw a definitive conclusion.

Comparison of group 2 (operated NSTI) to group 3 (non-operated suspected NSTI)

When comparing group 2 with group 3, we found that pain, high urea and creatinine levels,

Table 3. Microbiological identification among different groups of patients.

	NSTI with surgery ($n = 26$)	Non-NSTI ($n = 91$)	NSTI without surgery ($n = 8$)
Staphylococcus	6	15	1
Group A streptococcus	4	3	0
Other Streptococcus species	4	6	0
Escherichia coli	4	4	0
Enterobacteriaceae others than *Escherichia coli*			
Klebsiella	1	1	0
Citrobacter	1	0	0
Morganella	1	1	0
Enterobacter	2	3	1
Bacteroides	2	0	0
Others gram-negative	0	4	0
Enterococcus	1	5	0

microbiological identification were statistically more common in group 2 vs. group 3. LRINEC score and modified LRINEC score were not statistically different between the two groups. The LOS was higher in group 2 vs. group 3 (34 days (20–42) vs. 14 days (11–19), $p = .005$), while the 30-day in-hospital mortality and the number of amputations were not different between the two groups.

Comparison of group 1 (non-NSTI) with group 3 (non-operated suspected NSTI)

When comparing groups 1 and 3, the only differences were that group 3 tended to have statistically more fever, tachycardia and necrosis as assessed by MRI. LRINEC and modified LRINEC scores were not statistically different between the two groups.

Univariate and multivariate analysis

In the univariate analysis, a statistically significant relationship with surgery was found for the following variables: skin necrosis (OR 7.02; 95%CI: 1.40–35.2), heart rate (OR 1.04; 95%CI: 1.01–1.06), CRP (OR 1.02; 95%CI: 1.01–1.012), hyperglycemia (OR 1.01; 95%CI: 1.001–1.013), necrosis as assessed by MRI (OR 4.99; 95%CI: 1.52–15.9), LRINEC score (OR 1.20; 95%CI: 1.02–1.40) and modified LRINEC score (OR 1.11, 95%CI: 0.96–1.27).

Following multivariate analysis, we were able to assess several independent variables associated with surgery and observed that skin necrosis (OR 16.9, 95%CI: 2.2–131), tachycardia (OR 1.05, 95%CI: 1.02–1.09), CRP value at admission (OR 1.01, 95%CI: 1.002–1.013) and hyperglycemia (OR 1.01, 95%CI: 1.001–1.016) remained predictive for surgery.

A performance analysis revealed areas under a curve of 0.65 (95%CI: 0.48–0.74) as to the LRINEC score capacity for the use of surgery. The AUC of variables retained in the multivariate models was assessed (see Table 4). The AUC for a predictive model associating those four variables (heart rate, skin necrosis, CRP and glycemia at admission) was 0.71 (95%CI: 0.59–0.84) (Figure 1). However, the pairwise comparison of the AUC of LRINEC with the model built by associating the four variables did not reveal a statistically significant difference.

Discussion

The distinction between severe non-NSTI and NSTI requiring surgery based on clinical presentation, laboratory parameters, LRINEC score and imaging remains challenging in clinical practice. In our study, we observed clinical findings (skin necrosis, tachycardia), laboratory parameters (high CRP, hyperglycemia and hyponatremia, microbiological identification) and radiological data (necrosis on MRI), were significantly more likely in NSTI-patients requiring surgery. In our multivariate analysis, risk factors for surgery were skin necrosis, tachycardia, CRP value at admission, and hyperglycemia. However, the eight patients belonging to our group 3, although identified using those criteria as having NSTI, had a favorable evolution without surgery. The patients in this group are probably non-NSTI (but severe soft tissue infection without necrosis) and confirm that classifying the different entities of sSSTI still represents a difficult challenge.

Interestingly, we observed that pain, high urea, creatinine levels and microbiological identification were statistically more common in patients with NSTI who were operated on than in this group who were not operated on. On the contrary, this group tends to have statistically more fever, tachycardia and necrosis as assessed in MRI than group 1. Previous work corroborates the difficulty in expediently diagnosing NSTI [19–21]. Only 14–39% of NF is correctly identified at initial presentation [19–21]. In their study, Howell et al. comparing patients identified as having NSTI or not

Table 4. Univariate and multivariate analysis for identifying variables associated with surgery.

Variables	Odds ratio (95%CI)	*p* Value	Adjusted odds ratio (95%CI)	*p* Value
Age	1.00 (0.97–1.03)	.83		
Sex (male)	1.23 (0.49–3.01)	.65		
Pain	2.15 (0.76–6.01)	.15		
Redness	0.40 (0.03–4.61)	.46		
Skin necrosis (clinically)	7.02 (1.4–35.2)	.02	16.99 (2.19–131)	.007
Hypoesthesia	0.37 (0.04–3.78)	.40		
Heart rate	1.04 (1.01–1.06)	.01	1.05 (1.02–1.09)	.004
Systolic blood pressure	1.00 (0.97–1.04)	.92		
Diastolic blood pressure	0.97 (0.44–1.06)	.44		
CRP	1.02 (1.01–1.012)	.004	1.01 (1.002–1.013)	.01
Hemoglobin	1.12 (0.88–1.44)	.36		
NLR	1.06 (0.99–1.11)	.07		
LDH	1.01 (0.99–1.02)	.12		
Glycemia	1.01 (1.00–1.013)	.04	1.01 (1.001–1.016)	.02
Urea	1.01 (0.99–1.02)	.30		
Creatinine	1.01 (0.74–1.37)	.95		
Hyponatremia	0.89 (0.80–1.01)	.06		
CPK	1.01 (0.99–1.02)	.42		
Polymicrobial sepsis	3.60 (1.10–11.78)	.034		
Weight	1.00 (0.99–1.02)	.71		
Necrosis at MRI	4.99 (1.52–15.99)	.01		
LRINEC score	1.20 (1.02–1.40)	.036		
Modified LRINEC score	1.11 (0.96–1.27)	.14		
Cancer	0.30 (0.06–1.53)	.14		
Diabetes	1.48 (0.34–4.10)	.45		
Cardiac insufficiency	2.21 (0.65–7.55)	.20		
Hypertension	1.18 (0.47–2.93)	.72		
Peripheral arteriopathy	0.63 (0.21–1.83)	.39		
Chronic corticosteroid use	0.78 (0.20–3.10)	.72		
Chemotherapy	0.59 (0.05–6.81)	.67		
Immunosuppression	1.26 (0.36–4.30)	.72		
Alcohol abuse	0.88 (0.39–1.98)	.77		
Lymphoedema	0.79 (0.12–5.04)	.80		
Fever	1.03 (0.99–1.06)	.09		

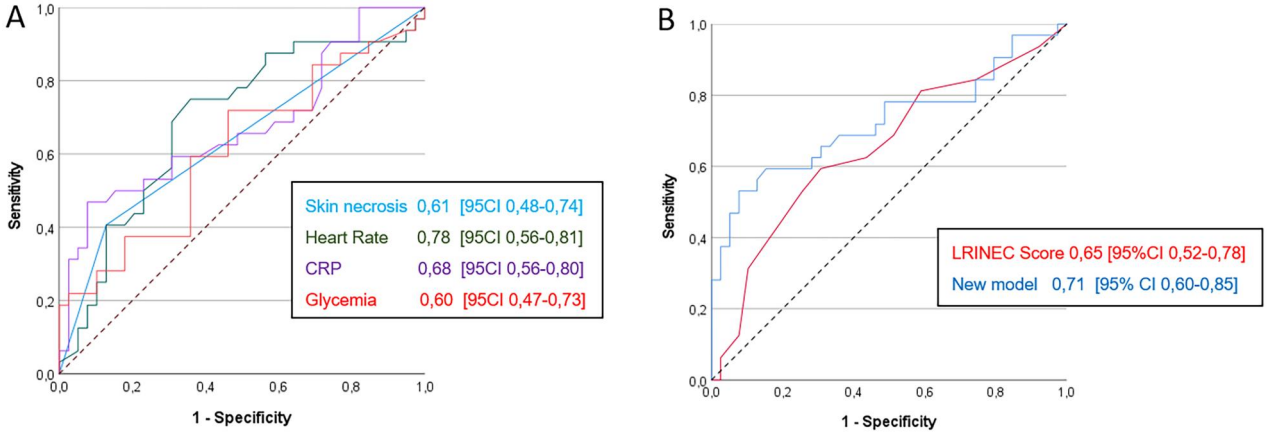


Figure 1. Receiver-operating characteristic curves (ROC) of estimated models for the use of surgery. Red: ROC for LRINEC; blue: ROC for model associating skin necrosis, tachycardia, C-reactive protein (CRP) value and hyperglycemia, green: reference line. Following multivariate analysis, we were able to assess several independent variables associated with surgery and observed that skin necrosis, tachycardia, CRP value at admission, and hyperglycemia remained predictive for surgery. A performance analysis revealed areas under a curve of 0.65 (95%CI: 0.48–0.74) as to the LRINEC score capacity for the use of surgery. The AUC of variables retained in the multivariate models was assessed. The AUC for a predictive model associating those four variables (heart rate, skin necrosis, CRP and glycemia at admission) was 0.71 (95%CI: 0.59–0.84) (A). However, the pairwise comparison of the AUC of LRINEC with the model built by associating the four variables did not reveal a statistically significant difference (B).

(non-NSTI) based on surgical findings at the initial operation, found indistinguishable degrees of fever and tachycardia, with remarkably similar rates of septic shock. Both groups saw 'Hard signs' of NSTI such as bullae, violaceous changes and crepitus, demonstrating that these rigid signs can also be present in patients with non-NSTI, making diagnosis even more challenging [6]. Fernando et al. also found that the lack of pathognomonic physical examination findings was insufficient to rule out NSTI [16].

In our study, when performing LRINEC score and modified LRINEC score, those scores were higher in NSTI group compared to non-NSTI group (LRINEC score (6.2 ± 2.7 vs. 3.9 ± 2.6, $p < .001$) and modified LRINEC score (10.6 ± 4.3 vs. 7.1 ± 3.6, $p < .001$)). However, in some studies, LRINEC scores failed to predict NSTI accurately [12,13]. Although LRINEC score and modified LRINEC score are helpful, they cannot be the only criteria guiding the surgical decision. The ROC curves in our model associating the four predictive variables (glycemia, skin necrosis, CRP and heart rate) showed the better performance to discriminate for the need for surgery. Even if the difference between our new model and the LRINEC is not statistically different, the variables introduced in our model all have a significant OR in multivariate analysis.

Some authors have shown that CK tends to be higher in NSTI than cellulitis [22,23]. Our study revealed a trend of CK that was higher in group 2 when compared to group 1 but without reaching statistical significance due to a substantial dispersion of values in group 2 (median [IQR] 119 [38–450] vs. 71 [45–123]). No difference was seen between groups 2 and 3 for CK. CK was not a risk factor in univariate analysis or multivariate analysis.

Among the MRI findings, we observed that necrosis presence was more often associated with NSTI. Imaging tests play a questionable role in diagnosing NSTI (particularly NF), and their availability should not delay the operative management [24,25]. On MRI, the primary abnormality found in NF is the thickening of the deep fasciae, with high signal intensity on fluid-sensitive sequences and heterogeneous enhancement after contrast material injection resulting from fluid accumulation and hyperemia along with necrotic fasciae. Muscle changes may also occur, generally in a superficial and limited manner, probably due to endomysium infiltration. There are considerable discrepancies in the MRI evaluation of NF. Several vital points deserve emphasis: (a) the absence of MRI abnormalities of the deep intermuscular fascia and connective tissue of the muscles rules out NF, (b) the presence of gas along the deep fasciae is peculiar but not sensitive, (c) the extensive thickening of the intermuscular fasciae with an appearance suggesting incomplete vascularization supports the diagnosis of NF and (d) the presence of alterations confined to the deep peripheral fascia and limited portions of the adjacent intermuscular fasciae is of borderline significance [24–27]. However, no single criterion was highly accurate. MRI is too sensitive and may lead to negative surgical exploration. For example, in a study of 22 patients with a high signal from the deep fasciae on T2 images, only one patient had NF. The diagnoses in the 21 other patients included abscess and cellulitis radiation-induced damage, osteomyelitis, and a ruptured popliteal cyst [28]. Interesting, when comparing group 1 to group 3 in our study, the two groups were similar, but group 3 had more necrosis described on MRI (2/91 (2.19%) in group 1 vs. 5/8 (62%) in group 3). Howell et al. found 20% of negative exploration in patients identified as NSTI [6].

In terms of outcome, mortality does not differ between non-NSTI and NSTI, overall LOS and the number of amputations remain higher in the NSTI group in our study compared to the two other groups, but the number was too low to draw a definitive conclusion. In our hospital, apart from the urgent cases, all cases with high suspicion of NSTI are discussed by a multidisciplinary team involving an experienced infectiologist, a plastic or orthopedic surgeon, and a radiologist with the decision to perform early surgery (within 24 h) being taken on a case by case basis. This may explain why the mortality rate is low in our study. Chao et al. showed also that rapid surgery within 12 h of admission combined with adequate medical therapy is important for treatment of sSSTI [29]. Howell et al. also found that the overall in-hospital mortality did not differ between NSTI and non-NSTI patients. Patients with NSTI had a longer intensive care unit LOS and a longer overall LOS. They also found significantly more amputations performed for patients with NSTI [6]. Patients with NSTI and those with non-NSTI had similar mortality indicating that severe cellulitis can also be a severe disease process. The increased LOS is likely secondary to numerous factors as patients with NSTI require substantial resources during their treatment.

Limitations

A major limitation is the difference in patient's numbers in the three groups compared and retrospective design of the study so that we cannot exclude bias in the classification of different groups. The second limitation is that details on treatment, such as type of antibiotic, duration of antibiotic, number of debridement, or complementary treatment, are not provided. These details influence the outcome globally. However, our study provided supplementary arguments of the difficulties in classifying or treating severe sSSTI, especially the decision to perform surgery even with the best clinical judgment. We also provided an alternative model score to

the LRINEC with a better AUC. In our model, glycemia was a predictive factor for surgery (NSTI) but the values of glycemia were higher in diabetic compared to non-diabetic patients ($p < .001$) meaning that diabetes contribute largely to the disturbances of glycemia. This model needs prospective and external validation.

Conclusions

The distinction between severe non-NSTI and NSTI requiring surgery remains challenging clinical practice. Our study found several clinical characteristics, laboratory and MRI findings that can help to distinguish non-NSTI and NSTI as described in the literature. The LRINEC score was identified as a risk factor for surgery, but in multivariate analysis, only four clinical and laboratory findings (glycemia, CRP, skin necrosis and heart rate) were associated with the need for surgery. Although the LRINEC score performed well in predicting surgery, the AUC of a model combining the four predictive variables was superior. Further research is needed to compare it with other models. In-hospital mortality at 30-day was similar between non-NSTI and NSTI, but LOS was longer in NSTI patients.

Author contributions

Contributions: JCY, AM and HY: conceptions, data collection. All authors wrote and corrected the manuscript. DC: statistical analysis.

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References

[1] Hersh AL, Chambers HF, Maselli JH, et al. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. Arch Intern Med. 2008;168(14):1585–1591. doi: 10.1001/archinte.168.14.1585.

[2] Stevens DL, Bryant AE. Necrotizing soft-tissue infections. N Engl J Med. 2017;377(23):2253–2265. doi: 10.1056/NEJMra1600673.

[3] Sarani B, Strong M, Pascual J, et al. Necrotizing fasciitis: current concepts and review of the literature. J Am Coll Surg. 2009;208(2):279–288. doi: 10.1016/j.jamcollsurg.2008.10.032.

[4] Yaghoubian A, de Virgilio C, Dauphine C, et al. Use of admission serum lactate and sodium levels to predict mortality in necrotizing soft-tissue infections. Arch Surg. 2007;142(9):840–846. doi: 10.1001/archsurg.142.9.840.

[5] Mills MK, Faraklas I, Davis C, et al. Outcomes from the treatment of necrotizing soft-tissue infections: results from the National Surgical Quality Improvement Program Database. Am J Surg. 2010;200(6):790–797, discussion 796–797. doi: 10.1016/j.amjsurg.2010.06.008.

[6] Howell EC, Keeley JA, Kaji AH, et al. Chance to cut: defining a negative exploration rate in patients with suspected necrotizing soft tissue infection. Trauma Surg Acute Care Open. 2019;4(1):e000264. doi: 10.1136/tsaco-2018-000264.

[7] Wall DB, de Virgilio C, Black S, et al. Objective criteria may assist in distinguishing necrotizing fasciitis from nonnecrotizing soft tissue infection. Am J Surg. 2000;179(1):17–21. doi: 10.1016/s0002-9610(99)00259-7.

[8] Wall DB, Klein SR, Black S, et al. A simple model to help distinguish necrotizing fasciitis from nonnecrotizing soft tissue infection. J Am Coll Surg. 2000;191(3):227–231. doi: 10.1016/s1072-7515(00)00318-5.

[9] Wong C-H, Khin L-W, Heng K-S, et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) Score is a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med. 2004;32(7):1535–1541. doi: 10.1097/01.ccm.0000129486.35458.7d.

[10] Borschitz T, Schlicht S, Siegel E, et al. Improvement of a clinical score for necrotizing fasciitis: 'pain out of proportion' and high CRP levels aid the diagnosis. PLOS One. 2015;10(7):e0132775. doi: 10.1371/journal.pone.0132775.

[11] Yildiz H, Yombi JC. Necrotizing soft-tissue infections. N Engl J Med. 2018;378(10):970. doi: 10.1056/NEJMc1800049.

[12] Neeki MM, Dong F, Au C, et al. Evaluating the laboratory risk indicator to differentiate cellulitis from necrotizing fasciitis in the emergency department. West J Emerg Med. 2017;18(4):684–689. doi: 10.5811/westjem.2017.3.33607.

[13] Wilson MP, Schneir AB. A case of necrotizing fasciitis with an LRINEC score of zero: clinical suspicion should trump scoring systems. J Emerg Med. 2013;44(5):928–931. doi: 10.1016/j.jemermed.2012.09.039.

[14] vanStigt SF, de Vries J, Bijker JB, et al. Review of 58 patients with necrotizing fasciitis in The Netherlands. World J Emerg Surg. 2016;11:21.

[15] Holland MJ. Application of the Laboratory Risk Indicator in Necrotising Fasciitis (LRINEC) score to patients in a tropical tertiary referral Centre. Anaesth Intensive Care. 2009;37(4):588–592. doi: 10.1177/0310057X0903700416.

[16] Fernando SM, Tran A, Cheng W, et al. Necrotizing soft tissue infection: diagnostic accuracy of physical examination, imaging, and LRINEC score: a systematic review and meta-analysis. Ann Surg. 2019;269(1):58–65. doi: 10.1097/SLA.0000000000002774.

[17] Gelbard RB, Ferrada P, Yeh DD, et al. Optimal timing of initial debridement for necrotizing soft tissue infection: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2018;85(1):208–214. doi: 10.1097/TA.0000000000001857.

[18] Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft

tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):e10–e52. doi: 10.1093/cid/ciu296.

[19] Wong CH, Chang HC, Pasupathy S, et al. Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am. 2003;85(8):1454–1460. doi: 10.2106/00004623-200308000-00005.

[20] Haywood CT, McGeer A, Low DE. Clinical experience with 20 cases of group a *Streptococcus* necrotizing fasciitis and myonecrosis: 1995 to 1997. Plast Reconstr Surg. 1999; 103(6):1567–1573. doi: 10.1097/00006534-199905060-00003.

[21] Hsiao CT, Weng HH, Yuan YD, et al. Predictors of mortality in patients with necrotizing fasciitis. Am J Emerg Med. 2008;26(2):170–175. doi: 10.1016/j.ajem.2007.04.023.

[22] Simonart T, Nakafusa J, Narisawa Y. Serum creatine phosphokinase level is important in the early diagnosis and microbiological evaluation of necrotizing fasciitis. J Eur Acad Dermatol Venereol. 2004;18(6):687–690. doi: 10.1111/j.1468-3083.2004.01108.x.

[23] Simon T, Simonart JM, Derdelinckx I, et al. Value of standard laboratory tests for the early recognition of group a beta-hemolytic streptococcal necrotizing fasciitis. Clin Infect Dis. 2001;32(1):E9–E12. doi: 10.1086/317525.

[24] Kirchgesner T, Tamigneaux C, Acid S, et al. Fasciae of the musculoskeletal system: MRI findings in trauma, infection and neoplastic diseases. Insights Imaging. 2019;10(1):47. doi: 10.1186/s13244-019-0735-5.

[25] Malghem J, Lecouvet FE, Omoumi P, et al. Necrotizing fasciitis: contribution and limitations of diagnostic imaging. Joint Bone Spine. 2013;80(2):146–154. doi: 10.1016/j.jbspin.2012.08.009.

[26] Yu JS, Habib P. MR imaging of urgent inflammatory and infectious conditions affecting the soft tissues of the musculoskeletal system. Emerg Radiol. 2009;16(4):267–276. doi: 10.1007/s10140-008-0786-2.

[27] Kim KT, Kim YJ, Won Lee J, et al. Can necrotizing infectious fasciitis be differentiated from nonnecrotizing infectious fasciitis with MR imaging? Radiology. 2011;259(3):816–824. doi: 10.1148/radiol.11101164.

[28] Loh NN, Ch'en IY, Cheung LP, et al. Deep fascial hyperintensity in soft-tissue abnormalities revealed by T2-weighted MR imaging. AJR Am J Roentgenol. 1997;168(5):1301–1304. doi: 10.2214/ajr.168.5.9129430.

[29] Chao WN, Tsai CF, Chang HR, et al. Impact of timing of surgery on outcome of *Vibrio vulnificus*-related necrotizing fasciitis. Am J Surg. 2013;206(1):32–39. doi: 10.1016/j.amjsurg.2012.08.008.