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What Demographic and Clinical Factors Are Associated with In-hospital Mortality in Patients with Necrotizing Fasciitis?

Jaret Karnuta MS, Joseph Featherall MD, Joshua Lawrenz MD, Jaymeson Gordon, Joshua Golubovsky BS, Jonah Thomas MS, Deepak Ramanathan MBBS, Claus Simpfendorfer MD, Lukas M. Nystrom MD, Maja Babic MD, Nathan W. Mesko MD

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Abstract

Background Necrotizing fasciitis is a rare infection with rapid deterioration and a high mortality rate. Factors associated with in-hospital mortality have not been thoroughly evaluated. Although predictive models identifying the diagnosis of necrotizing fasciitis have been described (such as the Laboratory Risk Indicator for Necrotizing Fasciitis [LRINEC]), their use in predicting mortality is limited.

Questions/purposes (1) What demographic factors are associated with in-hospital mortality in patients with necrotizing fasciitis? (2) What clinical factors are associated with in-hospital mortality? (3) What laboratory values are associated with in-hospital mortality? (4) Is the LRINEC score useful in predicting mortality?

Methods We retrospectively studied all patients with necrotizing fasciitis at our tertiary care institution during a 10-year period. In all, 134 patients were identified; after filtering out patients with missing data (seven) and those without histologically confirmed necrotizing fasciitis (12), 115 patients remained. These patients were treated with early-initiation antibiotic therapy and aggressive surgical intervention once the diagnosis was suspected. Demographic data, clinical features, laboratory results, and treatment variables were identified. The median age was 56 years and 42% of patients were female. Of the 115 patients analyzed, 15% (17) died in the hospital. Univariate and receiver operating characteristic analyses were performed due to the low number of mortality events seen in this cohort.

Results The demographic factors associated with in-hospital mortality were older age (median: 64 years for nonsurvivors [interquartile range (IQR) 57-79] versus 55 years for survivors [IQR 45-63]; p = 0.002), coronary artery disease (odds ratio 4.56 [95% confidence interval (CI) 1.51 to 14]; p = 0.008), chronic kidney disease (OR 4.92 [95% CI 1.62 to 15]; p = 0.006), and transfer from an outside hospital (OR 3.47 [95% CI 1.19 to 10]; p = 0.02). The presenting

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This work was performed in the Cleveland Clinic Health System, Cleveland, OH, USA.

J. Karnuta, J. Golubovsky, J. Thomas, Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA

J. Featherall, J. Lawrenz, J. Gordon, D. Ramanathan, L. M. Nystrom, N. W. Mesko, Department of Orthopaedic Surgery, Cleveland Clinic, Cleveland, Ohio, USA

C. Simpfendorfer, Department of Diagnostic Radiology, Cleveland Clinic, Cleveland, OH, USA

M. Babic, Department of Infectious Disease, Cleveland Clinic, Cleveland, OH, USA

N. W. Mesko (✉), Department of Orthopaedic Surgery, Orthopaedic and Rheumatologic Institute, Mail Code A41, 9500 Euclid Avenue, Cleveland, OH 44195, USA, Email: meskon@ccf.org; nate.mesko@gmail.com

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clinical characteristics associated with in-hospital mortality were positive initial blood culture results (OR 4.76 [95% CI 1.59 to 15]; p = 0.01), lactic acidosis (OR 4.33 [95% CI 1.42 to 16]; p = 0.02), and multiple organ dysfunction syndrome (OR 6.37 [95% CI 2.05 to 20]; p = 0.002). Laboratory values at initial presentation that were associated with in-hospital mortality were platelet count (difference of medians -136 [95% CI -203 to -70]; p < 0.001), serum pH (difference of medians -0.13 [95% CI -0.21 to -0.03]; p = 0.02), serum lactate (difference of medians 0.90 [95% CI 0.40 to 4.80]; p < 0.001), serum creatinine (difference of medians 1.93 [95% CI 0.65 to 3.44]; p < 0.001), partial thromboplastin time (difference of medians 8.30 [95% CI 1.85 to 13]; p = 0.03), and international normalized ratio (difference of medians 0.1 [95% CI 0.0 to 0.5]; p = 0.004). The LRINEC score was a poor predictor of mortality with an area under the receiver operating characteristics curve of 0.56 [95% CI 0.45-0.67].
Conclusions Factors aiding clinical recognition of necrotizing fasciitis are not consistently helpful in predicting mortality of this infection. Identifying patients with potentially compromised organ function should lead to aggressive and expedited measures for diagnosis and treatment. Future multicenter studies with larger populations and a standardized algorithm of treatment triggered by high clinical suspicion can be used to validate these findings to better help prognosticate this potentially fatal diagnosis.
Level of Evidence Level III, therapeutic study.

Introduction

Necrotizing soft-tissue infections are a distinct group of diseases that are associated with severe morbidity and high proportion of mortality [12]. Of these, necrotizing fasciitis is the most feared and is associated with invasion of the muscle fascia and quick spread to adjacent structures [15]. Prompt diagnosis must be made in a rapidly deteriorating patient, which can be complicated by the substantial variability in clinical presentation of necrotizing fasciitis. Clinical suspicion and diagnosis of necrotizing fasciitis is critical for immediate management, including transfer to an appropriate treatment facility [19], intensive care unit placement, appropriate antibiotic therapy [13, 25], and surgical débridement or amputation. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was introduced to assist in the timely diagnosis and treatment of necrotizing fasciitis [20]. The LRINEC score is a composite based on the following serum laboratory values: C-reactive protein, white blood cell count, hemoglobin, sodium, creatinine, and glucose, with higher values indicating more severe clinical deterioration. The initial study describing the LRINEC score used a small cohort of 89 patients with necrotizing fasciitis and established a cutoff score of 6 of 13 as a sensitive rubric for distinguishing necrotizing fasciitis from other, less severe soft tissue infections [35].

Some studies have attempted to use the same scoring system as a prognostic indicator, albeit with limited success [10, 11]. Additionally, the LRINEC score has not been shown to correlate with the severity of necrotizing soft-tissue infection using biological markers of infection and immunologic response [16]. Few studies have evaluated in detail the factors that may be associated with in-hospital mortality in patients with necrotizing fasciitis, a deadly disease with high mortality rates between 12% and 26% [1, 3, 21, 22, 34]. A small study of 70 patients with necrotizing fasciitis found hypotension (systolic pressure ≤ 90 mm Hg), low leukocyte counts, low segmented leukocyte counts, low platelet counts, low serum albumin levels, and high band-form leukocytes to be predictive of mortality [33]. However, this study was limited by a small cohort and focused solely on necrotizing fasciitis caused by *Vibrio* infections. A Nationwide Inpatient Sample database study of 9958 patients identified transfer status as a predictor of mortality for patients admitted with necrotizing fasciitis; however, this study was limited by its inability to capture laboratory and other clinical data [19]. A large, international study of 331 patients with necrotizing fasciitis identified age, diabetes mellitus, hypertension, coronary artery disease, and sacral infections as more prevalent in non-survivors [22]. This same study found high creatinine and LRINEC scores, along with lower hemoglobin, platelet, and blood glucose levels, were associated with mortality. It is unclear if this study's findings can be replicated in other countries and patient populations. Another large, international study of 472 patients identified liver cirrhosis, soft tissue air, *Aeromonas* infection, age, band neutrophils, elevated partial thromboplastin time, bacteremia, and elevated serum creatinine as predictors of mortality [21]. This study similarly is localized to a specific population, and it is unclear if these findings can be extrapolated to different populations. A study of 150 patients with necrotizing soft tissue infections (of which necrotizing fasciitis is a subset) found that elevated blood urea nitrogen, potassium, creatinine, partial thromboplastin time, leukocyte count, and aspartate aminotransferase, along with lower pH and bicarbonate levels, were associated with an increased mortality risk [29]. Other factors previously associated with mortality include a history of metabolic syndrome (for example, heart disease, diabetes, obesity), increased age, sepsis at presentation, confirmed clostridial infection, surgical intervention greater than 24 hours, and infections involving the head, neck, or trunk [1, 2, 4, 7, 14, 21, 34]. As mentioned, few studies have identified risk factors for in-hospital mortality in patients with pathologically confirmed necrotizing fasciitis [19, 21, 22, 33]. Given the rapid progression of necrotizing fasciitis and its associated high mortality risk, it is critical to understand the factors that predispose individuals to mortality during their hospitalization.

Therefore, we asked, (1) What demographic factors are associated with in-hospital mortality in patients with

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necrotizing fasciitis? (2) What clinical factors are associated with in-hospital mortality? (3) What laboratory values are associated with in-hospital mortality? (4) Is the LRINEC score useful in predicting mortality?

Patients and Methods

Patient Selection

After institutional review board approval, all patients with necrotizing fasciitis presenting to an integrated health system between March 2009 and March 2019 were retrospectively identified and studied. Each individual's operative report and pathology report was reviewed. We included patients with all of the following: (1) signs of infection below the level of the investing fascia as described in the operative report, (2) a postoperative diagnosis of necrotizing fasciitis by the operating surgeon, and (3) histologically confirmed necrosis below the level of the deep fascia.

All 134 patients who were treated for necrotizing fasciitis at our multihospital health system during a 10-year period were identified and included in the study. Overall, 115 patients remained after filtering out patients with missing data (seven) and those without histologically-confirmed necrotizing fasciitis (12) (Fig. 1). The median age of the cohort was 56 years (interquartile range 47-65), and 43% (49 of 115) of patients were female (Table 1).

Patient Demographic Data

Individuals not involved in patient care, one surgeon, and one infectious disease doctor collected patient demographic variables, including age at presentation, sex, race, BMI, and smoking history, directly from the patient's electronic medical record (Epic Systems, Verona, WI, USA) via retrospective chart review. The surgeon and infectious disease doctor were directly involved in patient care for a minority of patients. Transfer status was defined if the patient was transferred to our institution from an outside hospital via an ambulance or helicopter. Several medical comorbidities were also collected from the electronic medical record. Coronary artery disease was defined as a history of angina, myocardial infarction, or prior revascularization procedure. Diabetes was defined as a hemoglobin A1C level > 6.5 on record, history of pharmacologic treatment, or prior fasting glucose level ≥ 126 mg/dL. Intravenous drug use was

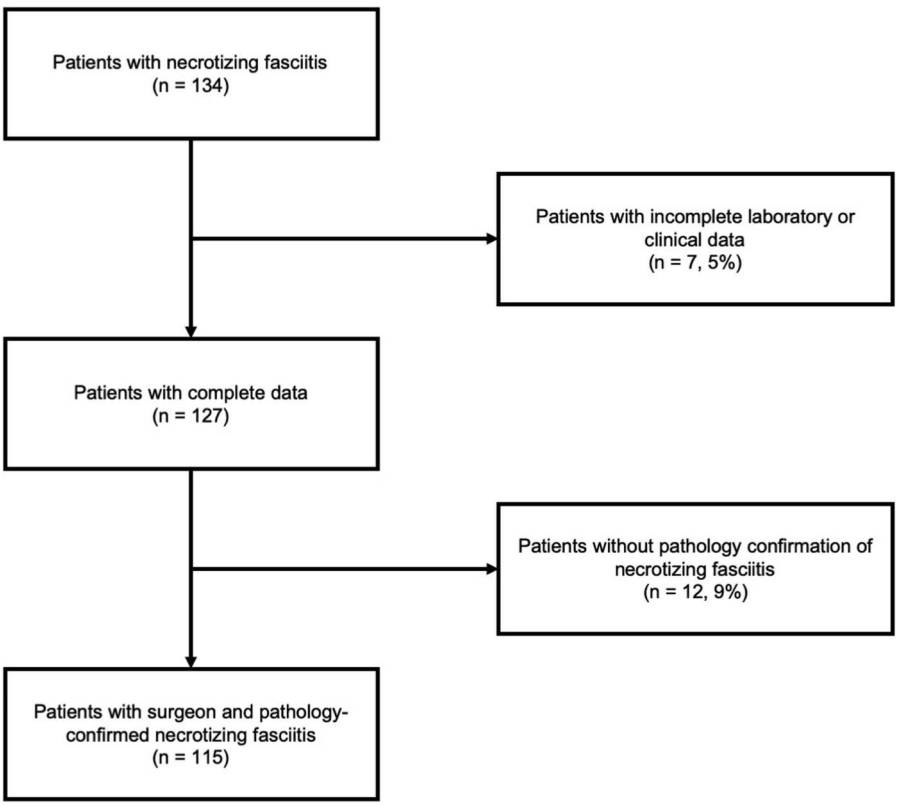

Fig. 1 The STROBE diagram for the cohort is shown here.

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Table 1. Demographics, clinical characteristics, and medical comorbidities

Variable	Overall	Survived hospitalization	In-hospital mortality	Difference of medians or odds ratio (95% CI)	p value
Number of patients	115	98	17		
Age (years), median (IQR)	56 (47-65)	55 (45-63)	64 (57-79)	9.50 (2.5 to 24)	0.002
Transferred to study institution	24% (28)	20% (20)	47% (8)	3.47 (1.19 to 10)	0.02
Race				1.12 (0.69 to 1.73)	0.48
White, non-Hispanic	64% (74)	65% (64)	59% (10)		
White, Hispanic	0.9% (1)	1% (1)	0% (0)		
Black	32% (37)	32% (31)	35% (6)		
Asian	1.7% (2)	1% (1)	5.9% (1)		
Other	0.9% (1)	1% (1)	0% (0)		
Female sex	43% (49)	44% (43)	35% (6)	0.70 (0.23 to 1.99)	0.60
BMI (kg/m^2), median (IQR)	32 (26-40)	31 (26-40)	32 (25-38)	1.50 (-7.42 to 6.97)	0.72
Diabetes	64% (74)	65% (64)	59% (10)	0.76 (0.27 to 2.26)	0.60
Smoking status				0.81 (0.43 to 1.53)	0.80
Never	30% (35)	30% (29)	35% (6)		
Former	33% (38)	33% (32)	35% (6)		
Current	37% (42)	38% (37)	29% (5)		
Coronary artery disease	21% (24)	16% (16)	47% (8)	4.56 (1.51 to 14)	0.008
Peripheral vascular disease	22% (25)	19% (19)	35% (6)	2.27 (0.71 to 6.78)	0.20
Chronic kidney disease	20% (23)	15% (15)	47% (8)	4.92 (1.62 to 15)	0.006
Immune modulator therapy	6.1% (7)	5.1% (5)	12% (2)	2.48 (0.33 to 13)	0.28
Intravenous drug use	3.5% (4)	3.1% (3)	5.9% (1)	1.98 (0.10 to 17)	0.48

All variables are reported as % (number) unless otherwise specified. The Mann-Whitney U test was used to compare continuous variables and Fisher's exact test was used to compare categorical variables. Strength of association is reported as an odds ratio for categorical variables or difference of medians for continuous variables.

defined as known use within the past year. Immune modulator therapy was gathered from the patient's medication list on admission. Patients were classified as having chronic kidney disease if they had Stage 3 or higher chronic kidney disease. Peripheral vascular disease was classified as proven disease on CT angiography, Doppler ultrasound, ankle brachial index, or angiogram. Study data were collected and managed using our institutional REDCap electronic data capture suite (Vanderbilt University, Nashville, TN, USA) [17, 18].

Clinical Data

Clinical characteristics of the infection, including initial presentation and intraoperative blood cultures, infection location, and the presence of gas on either radiography or CT, were extracted from the patient's electronic medical record. Laboratory values (white blood cell count, absolute neutrophil count, hemoglobin level, hematocrit level, platelet count, erythrocyte sedimentation rate, C-reactive protein level, serum albumin level, D-dimer level, serum potassium level, serum pH level, serum lactate level, serum creatinine level, serum glucose level, partial thromboplastin time, and international normalized ratio) were collected from the initial presentation, within 48 hours before the index surgery. For assessing the severity of sepsis, the worst clinical condition of the patient in the 48 hours before the index surgery was identified. Patients were classified as having sepsis if they met at least two of the criteria for systemic inflammatory response syndrome [9]. Patients were classified as having lactic acidosis if they had a serum lactic acid level > 4.0 mmol/L and a serum pH level < 7.35 [32]. Patients were classified as having multiple organ failure syndrome if they had evidence of failure of at least two organs based on laboratory values or physical exam as outlined in the multiple organ dysfunction score rubric [24]. Findings of subcutaneous gas on any imaging modality (radiography or CT) before surgery were extracted from radiology reports. Blood cultures at the initial presentation and intraoperative wound cultures were reviewed and classified as monomicrobial or polymicrobial. Survival to discharge was determined as the primary outcome variable.

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Treatment Considerations

In general, once the suspicion for necrotizing fasciitis was made, the patient was emergently transitioned to the operative theater, with the goal of less than 120 minutes from recognition to incision. Broad-spectrum intravenous antibiotics were started immediately on the floor if necrotizing fasciitis was suspected at the onset. Coverage for both *Streptococcus* and polymicrobial infection etiologies was considered, with strong consideration made to include clindamycin to cover Group A *Streptococcus*. Blood cultures, if available, helped to guide antibiotic therapy. In most patients, the surgeon started with a limited exposure to survey the superficial tissue, fascia, and deep muscle. Encountering clear "dishwater" fluid and necrotic fascia led to immediate wide exposure. In the operating room, the appearance of white, glistening fascia with aggressive skin/subcutaneous features was thought to represent a necrotizing skin infection, and not necrotizing fasciitis, and focus was placed on the subcutis alone in this situation. Frozen sections were sent but not used in isolation for making a diagnosis. In those patients where the soft tissue involvement was circumferential on a limb or involving vital structures (for example, major limb perfusing vessels, sciatic nerve, brachial plexus), the surgeon performed an amputation—all patients or surrogate decision makers were consented for a possible amputation before surgery. In those patients where limb salvage was performed, all suspicious tissue was removed and the wound temporized with either a negative pressure device or povidone-iodine-soaked gauze. All patients underwent redébridement within 12-48 hours, depending on the improvement in clinical status and regional clinical exam. Patients underwent serial débridement every 24 to 72 hours until laboratory numbers, vital signs, and pressor requirements showed a dramatic trending improvement. If possible, primary closure over drains occurred once the clinical picture improved, with larger defects allowed to heal with secondary intention healing or plastic surgery soft tissue reconstruction techniques. As our study was not designed to study the effect of treatment on mortality, we did not compare treatment characteristics between survivors and non-survivors. Of the 115 patients, the median number of surgeries per patient was three [IQR 2-4], with 35% (40) of patients requiring amputation (Table 2).

Table 2. Treatment characteristics for the patient cohort

Variable	Percent (total) or median (interquartile range)
Number of patients	115
Symptom to admission time (hours)	72 (39-138)
Admission to antibiotics time (hours)	2 (1-2)
Admission to surgery time (hours)	7 (4-14)
ICU LOS (days)	7 (3-14)
Hemodialysis	20 (23)
Clindamycin regimen	43 (49)
Initial amputation	24 (28)
Amputation as end surgery	35 (40)
Débridement	2 (1-4)
Total surgeries	3 (2-4)
Total follow-up (days)[a]	315 (115-1236)

[a]Follow-up days only include patients that survived to discharge.
All continuous variables are reported as median (interquartile range) and dichotomous variables are reported as percent (number). This study was not designed to study the association between treatment and mortality, so hypothesis testing was not performed on treatment characteristics; ICU = intensive care unit; LOS = length of stay.

Statistical Analysis

We used R statistical software version 3.5.2 (The R Foundation, Vienna, Austria) for all data analyses [30]. Continuous variables were determined to be non-normal using the Shapiro-Wilk test of normality. Comparisons of continuous variables between the in-hospital mortality and hospitalization survival groups were performed using the nonparametric Mann-Whitney U test, and the Fisher exact test was used for categorical variables. Odds ratios were calculated for mortality using univariable logistic regression. Difference of medians for continuous variables was calculated using the pairwise CI R package, which uses a bootstrap algorithm for confidence interval calculation (version 0.1-27). Univariate analyses were performed in series for each predictor. A multivariable analysis could not be used given the small number of mortality events in the dataset in an attempt to prevent data overfitting and to reduce sparse-data bias. It is a commonly accepted practice to use 10 events per variable for modeling a given outcome [26, 27]. Thus, we can only model one variable as the number of events (deaths) is 17. Univariable analyses prevent the disentanglement of confounding variables, so we present all findings as marginal associations which require studies with large number of mortality events to confirm. Area under the receiver operating characteristics curve (AUC) analysis of the LRINEC score was performed using the pROC package (version 1.12.1). Incremental LRINEC cutoff values between 0 and 13 were used and sensitivity and specificity values were calculated at each cutoff. A receiver operating characteristics curve was made and the AUC was calculated. AUCs can be interpreted as excellent (0.9-1.0), good

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(0.8-0.9), fair (0.7-0.8), poor (0.6-0.7), and no better than chance (0.5-0.6) [5]. A p value threshold of 0.05 was chosen for significance.

Results

Demographic Factors Associated with Mortality

The demographic factors associated with in-hospital mortality were older age (64 years [IQR 57-79] versus 55 years [IQR 45-63]; difference of medians 9.5 [95% CI 2.5 - 24]; p = 0.002), coronary artery disease (odds ratio 4.56 [95% CI 1.51 to 14]; p = 0.008), chronic kidney disease (OR 4.92 [95% CI 1.62 to 15]; p = 0.006), and initial diagnosis at another institution with subsequent transfer to our center (OR 3.47 [95% CI 1.19 to 10]; p = 0.02) (Table 1).

Clinical Factors Associated with Mortality

The presenting clinical characteristics associated with in-hospital mortality were positive initial blood culture results (OR 4.76 [95% CI 1.59 to 15]; p = 0.01), lactic acidosis (OR 4.33 [95% CI 1.42 to 16]; p = 0.02), and multiple organ dysfunction syndrome (OR 6.37 [95% CI 2.05 to 20]; p = 0.002) (Table 3). The most common primary site of infection was the lower extremity. Twelve of 115 patients (10%) had multiple anatomic regions as the primary source of infection, with all of these patients having a contiguous infection in the trunk, sacrum, and/or lower extremity.

Laboratory Values Associated with Mortality

Laboratory values at initial presentation that were associated with in-hospital mortality were platelet count (difference of medians -136 [95% CI -203 to -70]; p < 0.001), serum pH (difference of medians -0.13 [95% CI -0.21 to -0.03]; p = 0.02), serum lactate (difference of medians 0.90 [95% CI 0.40 to 4.80]; p < 0.001), serum creatinine (difference of medians 1.93 [95% CI 0.65 to 3.44]; p < 0.001), partial thromboplastin time (difference of medians 8.30 [95% CI 1.85 to 13]; p = 0.03), and international normalized ratio (difference of medians 0.1 [95% CI 0.0 to 0.5]; p = 0.004) (Table 4).

Laboratory Risk Indicator for Necrotizing Fasciitis Score and Mortality

There was no difference in LRINEC scores between survivors (8.00 [IQR 6.00 to 9.25]) and patients who died in the hospital (7.00 [IQR 5.50 to 7.75]; difference of medians: -1 [95% CI -2 to 1]; p = 0.43). The AUC for LRINEC was no better than chance at predicting in-hospital mortality with an AUC of 0.56 [95% CI 0.45 to 0.67] (Fig. 2).

Table 3. Clinical characteristics at initial presentation

Clinical characteristic variable	Survived hospitalization	In-hospital mortality	Odds ratio (95% CI)	p value
Number of patients	98	17		
Positive blood culture results at initial presentation	21% (20)	53% (9)	4.76 (1.59 to 15)	0.01
Polymicrobial blood culture results at initial presentation	4% (4)	5.9% (1)	0.50 (0.02 to 4.13)	>0.99
Polymicrobial intraoperative wound culture results	57% (56)	53% (9)	0.56 (0.19 to 1.65)	0.41
Infection location				
Neck	1% (1)	5.9% (1)	6.06 (0.23 to 159)	0.28
Trunk	11% (11)	18% (3)	1.70 (0.35 to 6.28)	0.43
Sacrum and back	36% (35)	18% (3)	0.42 (0.09 to 1.40)	0.26
Upper extremity	6.1% (6)	12% (2)	2.04 (0.28 to 9.88)	0.34
Lower extremity	56% (55)	65% (11)	1.43 (0.50 to 4.45)	0.60
Gas on imaging	72% (71)	65% (11)	0.70 (0.24 to 2.19)	0.57
Systemic inflammatory response syndrome	90% (88)	88% (15)	0.85 (0.20 to 5.90)	>0.99
Lactic acidosis	43% (42)	76% (13)	4.33 (1.42 to 16)	0.02
Multiple organ dysfunction syndrome	12% (12)	47% (8)	6.37 (2.05 to 20)	0.002

Data are presented as percent (number). Fisher's exact test was used to compare categorical variables. Odds ratios were calculated using logistic regression.

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Table 4. Laboratory values at initial presentation

Laboratory variable	Survived hospitalization	In-hospital mortality	Difference of medians (95% CI)	p value
Number of patients	98	17		
White blood cell count (K/uL)	17 (12-23)	16 (8.63-21)	-1.07 (-8.66 to 3.04)	0.17
Absolute neutrophil count (K/uL)	16 (9.71-21)	14 (5.32-19)	-2.13 (-12 to 3.17)	0.14
Hemoglobin level (g/dL)	11 (8.90-13)	9.3 (8.50-11)	-1.55 (-2.60 to 0.10)	0.07
Hematocrit level (%)	32 (26-37)	29 (27-33)	-2.20 (-5.40 to 1.70)	0.25
Platelet count (K/uL)	249 (157-337)	113 (56-172)	-136 (-203 to -70)	< 0.001
Erythrocyte sedimentation rate (mm/hour)	82 (58-98)	75 (26-97)	-7.00 (-69 to 42)	0.69
C-reactive protein (mg/dL)	25 (14-32)	11 (6.97-36)	-14 (-21 to 26)	0.89
Serum albumin level (g/dL)	2.5 (1.90-3.00)	2.4 (2.0-2.8)	-0.10 (-0.50 to 0.35)	0.74
D-dimer level (ng/mL)	3965 (3148-6035)	10,010 (4450-22,875)	6045 (-3355 to 30620)	0.34
Serum sodium level (mmol/L)	132 (129-136)	136 (130-137)	4 (-2 to 6)	0.13
Serum potassium level (mmol/L)	4 (3.50-4.40)	4 (3.40-5.10)	0.00 (-0.6 to 1.1)	0.47
Serum pH level	7.35 (7.25-7.41)	7.22 (7.16-7.32)	-0.13 (-0.21 to -0.03)	0.02
Serum lactate level (mmol/L)	1.7 (1.30-2.65)	2.60 (2.10-6.40)	0.90 (0.40 to 4.80)	< 0.001
Serum creatinine level (mg/dL)	1.22 (0.88-2.17)	3.15 (1.84-4.72)	1.93 (0.65 to 3.44)	< 0.001
Serum glucose level (mg/dL)	159 (117-293)	126 (78-213)	-33 (-83 to 50)	0.07
Partial thromboplastin time (seconds)	33 (30-38)	41 (34-46)	8.30 (1.85 to 13)	0.03
International normalized ratio	1.2 (1.1-1.3)	1.30 (1.20-1.70)	0.10 (0.0 to 0.5)	0.004
LRINEC score	8 (6-9.25)	7 (5.50-7.75)	-1 (-2 to 1)	0.43

All values are presented as the median (interquartile range). The Mann-Whitney U test was used to compare continuous variables; LRINEC = Laboratory Risk Indicator for Necrotizing Fasciitis.

Discussion

Current research on necrotizing fasciitis typically uses correlations derived from patients with necrotizing soft-tissue infection. There is a need to identify the demographic, clinical, and laboratory factors present on hospital admission to better delineate the expected trajectory of necrotizing fasciitis patients. Necrotizing fasciitis can be distinguished from similar, less severe infections using the LRINEC score, although there is no consensus as to the ability of this score to predict mortality. We found that increasing age, history of coronary artery disease, history of chronic kidney disease, and interhospital transfer were associated with an increased risk of death among patients with necrotizing fasciitis. We also found that positive blood culture results at initial presentation, sepsis, decreased blood pH level, elevated creatinine level, elevated lactate level, elevated prothrombin time, elevated international normalized ratio, and decreased platelet count likewise were associated with in-hospital mortality. However, we did not find the LRINEC to be useful to predict those patients who ultimately died from the infection.

This study had a number of important limitations. The most important limitation is the broad number of treatment providers and lack of treatment standardization. As this diagnosis requires timely treatment and is seen in emergent scenarios, there is a large population of providers on call that may be asked to clinically identify this diagnosis. Depending on comfort level for making a clinical diagnosis, diagnosis and treatment timing will vary greatly. These findings can only apply if the suggested algorithm of treatment is used, though it is important to note the retrospective nature of this study and the generalized treatment algorithm used due to a lack of standardization. Our institution is a tertiary care center with access to various surgical subspecialties in the hospital at all times and specialized providers who see this diagnosis multiple times per month. Our findings likely generalize to similarly equipped medical centers but will not be as applicable to centers with fewer resources and critical care support for gravely ill patients. We studied a relatively small cohort, which limited the number of variables that could be analyzed. Within our statistical framework, we were only able to perform univariable analyses. We were unable to untangle confounding variables and were similarly unable to identify independent predictors. Variable effect sizes presented herein are confounded and cannot be used to generate an overall risk of mortality given a specific presentation. Thus, these results should be viewed as preliminary and require large-scale follow-up studies to identify independent predictors. We were limited to the

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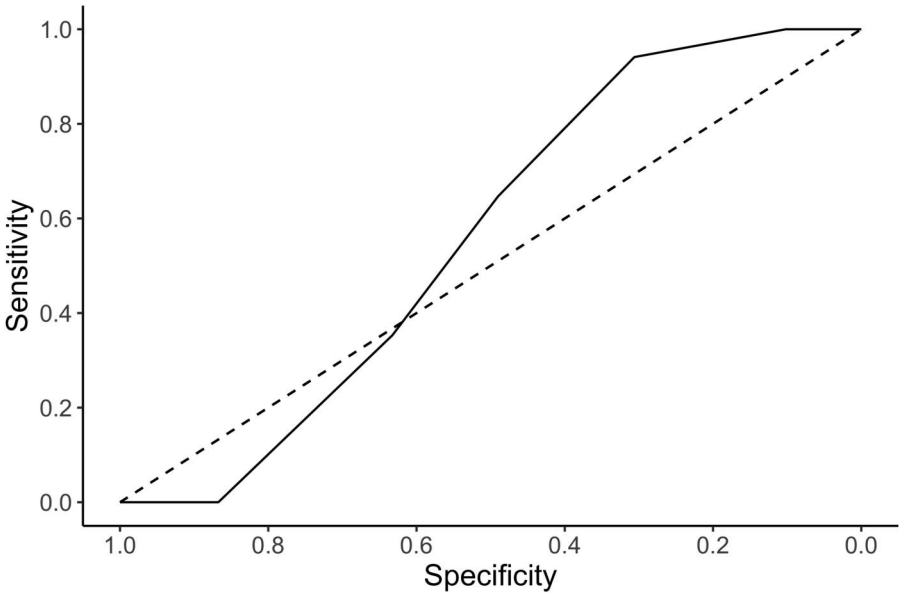

Fig. 2 Receiver operating characteristics (ROC) curve assessing the ability of the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score to predict mortality. The solid line represents the ROC for the LRINEC score. The dashed line represents a predictor that performs no better than chance with an area under the curve of 0.5.

documentation collected during admission and the treatment course and needed to rely on outside hospital records for many data points. Outside records are routinely requested and scanned into our electronic records system, which allows us to confirm data entered into our electronic medical record. Our electronic medical record had limitations as to what we could collect, and the data quality was limited because it relied on multiple parties (such as nurses, physicians, and laboratory technicians) entering data on every patient. This situation is common in the treatment of complex patients, and all of the medical personnel entering information are trained to maintain high-quality records. Our study was also retrospective, which restricted our data to only include variables collected by treating physicians. This limitation prevents us from identifying factors that are not routinely collected in the course of standard medical care, such as clinical rationale for treatment. These results will benefit from a prospectively collected study of necrotizing fasciitis patients.

We found that older age and history of multisystem disease was associated with a higher risk of in-hospital mortality. In a similar single-center study, age, the presence of two or more comorbidities, and increasing time to surgery were associated with in-hospital mortality [34]. In addition to age, we found that chronic kidney disease, coronary artery disease, sepsis before surgery, laboratory values, and hemodialysis were different between survivors and nonsurvivors. Coronary artery disease was similarly reported as being associated with mortality in an international study of necrotizing fasciitis [22]. Prior heart disease has also been found to be a predictor of mortality in patients with sepsis without necrotizing fasciitis [31]. Renal disease, defined in our cohort as Stage 3 or worse chronic kidney disease [8], has been shown to impair the host's immune defense and wound healing [6]. Transfer status has similarly been shown to impact mortality, suggesting that patients with suspected infection should be expeditiously transferred to a tertiary care center or initial surgical treatment should be provided at the diagnosing institution, if available [19].

Clinical presentation suggesting the involvement of systemic disease (positive blood culture results and multiple organ dysfunction syndrome) were associated with in-hospital mortality. Blood culture results at initial presentation were positive more frequently in patients who did not survive than in those who did. This finding indicates that multiple underlying factors could contribute to the rate of infection spread and mortality. Although the time from symptom presentation to admission was similar between the groups, increased positive blood culture results in the mortality group could mean a longer time from infection to administration, or infection with a more virulent organism. Deep invasion of bacteria into the primary blood supply of the infected regions resulted in increased bacterial dissemination into the blood stream. Increased bacterial depth and spread was also clinically seen as larger ulcerations. Patients with positive blood culture results could also have had weakened immune system function that was not captured by the variables we collected.

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Laboratory values suggestive of acute clinical decompensation and sepsis (platelet count, serum pH, serum lactate, serum creatinine, and coagulation studies) were associated with in-hospital mortality, although the LRINEC score derived from laboratory values was not found to be predictive of mortality. A small study similarly identified the association between low platelet counts and mortality [33]. However, this study also identified white blood cell counts to be predictive of mortality, a finding that we did not see. This discrepancy could be due to differences in infectious organism distribution. A retrospective study found high creatinine and LRINEC scores and low platelets were associated with mortality [22]. Creatinine levels trend closely with the severity of sepsis due to decreased renal perfusion results in acute kidney injury, which may lead to rapid decompensation in an already precariously ill patient [23]. This association with mortality has been shown in non-septic patients as well. In a study of patients with non-septic pneumonia, acute kidney injury correlated with mortality [28]. This finding suggests that kidney injury in the absence of profound sepsis may increase mortality risk. Partial thromboplastin time has been associated with mortality in a large-scale study, a finding replicated in our study [21]. This finding can be explained by either acute liver decompensation or consumption of clotting factors by sepsis-induced coagulopathy. Although certain laboratory values were associated with mortality, the LRINEC score demonstrated poor predictive ability in predicting in-hospital mortality.

Historically, it has been heralded as critical for providers to clinically suspect necrotizing fasciitis and reduce the time to antibiotic treatment. Patients with clear signs of infection that could develop into necrotizing fasciitis (such as deep purulent abscesses or cellulitis with systemic symptoms) should be monitored carefully. Providers should have a low threshold for rapid administration of parenteral antibiotics and expedite a clinical evaluation for necrotizing fasciitis, even if a surgeon provider is not comfortable in making the initial clinical call for an emergent operation. Although the time from admission to surgery was not substantial in our cohort, we believe that rapid surgery is necessary to preserve tissue, eradicate infection, and have patients survive the disease because previous studies have identified the time to surgery as an important factor to decrease mortality because of necrotizing fasciitis [25].

In conclusion, increasing age; history of renal disease; history of cardiac artery disease; interhospital transfer; positive blood culture results preoperatively; severe sepsis at the time of admission; increased rate of initial amputation, lactate levels, creatinine levels, prothrombin time, and international normalized ratios; and decreased blood pH levels and platelet counts were all found in patients who died during their hospitalization for necrotizing fasciitis. However, the LRINEC score did not distinguish patients at risk for death from those who survived. These findings can be used to counsel patients and families on mortality risk, giving them warning of possible decompensation and time to discuss care goals. Importantly, surgeons should not rely on the diagnostic LRINEC as a prognostic factor. Instead, providers should recognize the constellation of clinical and laboratory findings suggestive of acute decompensation as well as those patients who may have lower-end organ reserve (such as patients with cardiac and kidney disease). Being overly aggressive and taking patients to the operating room for clinical exploration and biopsy may be considered for those patients where the diagnosis is not decisive. Finally, these findings can be applied to build a multivariable predictive model of necrotizing fasciitis in future multicenter studies when larger numbers can be acquired. Building such a tool will require many more patients, and would benefit from multi-institutional cooperation or the use of insurance or country-wide registries. The difficulty for future studies, however, is creating a standardized approach to a process that has an unpredictable, emergent timing of presentation and physicians with different comfort levels for making the clinical diagnosis.

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