PAPER

Immunocompromised Status in Patients With Necrotizing Soft-Tissue Infection

Emily Z. Keung, MD; Xiaoxia Liu, MS; Afrin Nuzhad, BS; Christopher Adams, PharmD, BCPS; Stanley W. Ashley, MD; Reza Askari, MD

Importance: There is a scarcity of research on immunocompromised patients with necrotizing soft-tissue infection (NSTI).

Objective: To evaluate the effect of immunocompromised status in patients with NSTI.

Design and Setting: Single-institution retrospective cohort study at a tertiary academic teaching hospital affiliated with a major cancer center.

Participants: Patients with NSTI.

Exposure: Treatment at Brigham and Women's Hospital and Dana-Farber Cancer Institute between November 25, 1995, and April 25, 2011.

Main Outcome and Measure: Necrotizing soft-tissue infection–associated in-hospital mortality.

Results: Two hundred one patients were diagnosed as having NSTI. Forty-six were immunocompromised (as defined by corticosteroid use, active malignancy, receipt of chemotherapy or radiation therapy, diagnosis of human immunodeficiency virus or AIDS, or prior solid organ or bone marrow transplantation with receipt of chronic immunosuppression). At presentation, immunocompromised patients had lower systolic blood pressure (105 vs 112 mm Hg, $P=.02$), glucose level (124 vs 134 mg/dL, $P=.03$), and white blood cell count (6600/μL vs 17 200/μL, $P<.001$) compared with immunocompetent patients. Immunocompromised patients were less likely to have been transferred from another institution (26.1% vs 52.9%, $P=.001$), admitted to a surgical service (45.7% vs 83.2%, $P<.001$), or undergone surgical debridement on admission (4.3% vs 61.3%, $P=.001$). Time to diagnosis and time to first surgical procedure were delayed in immunocompromised patients ($P<.001$ and $P=.001$, respectively). Immunocompromised patients had higher NSTI-associated in-hospital mortality (39.1% vs 19.4%, $P=.01$).

Conclusions and Relevance: Immunocompromised status in patients with NSTI in this study is associated with delays in diagnosis and surgical treatment and with higher NSTI-associated in-hospital mortality. At presentation, immunocompromised patients may fail to exhibit typical clinical and laboratory signs of NSTI. Physicians caring for similar patient populations should maintain a heightened level of suspicion for NSTI and consider early surgical evaluation and treatment.

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Author Affiliations: Departments of Surgery (Drs Keung, Ashley, and Askari and Ms Nuzhad), Anesthesiology (Ms Liu), and Pharmacy (Dr Adams), Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

NECROTIZING SOFT-TISSUE infections (NSTIs) are surgical emergencies characterized by rapidly progressive soft-tissue necrosis and associated with significant morbidity and mortality. The first description is attributed to Hippocrates: "[T]he exciting cause was a trivial accident or a very small wound . . . the erysipelas would quickly spread widely in all directions. Flesh, sinews, and bones fell away in large quantities. . . . There were many deaths."[1(pS460)] Necrotizing soft-tissue infection encompasses a spectrum of disease involving various anatomical locations and depth of involvement known by many names, including hospital gangrene, necrotizing erysipelas, suppurative fasciitis, clostridial gangrene, gas gangrene, Fournier gangrene, Ludwig angina, and necrotizing fasciitis.[2] Although rare, with approximately 1000 cases per year and 0.04 cases per 1000 person-years in the United States,[3] the incidence of NSTI is increasing.[4] Despite advancements in our understanding of this disease and improvements in treatment, NSTI-associated mortality rates remain high, with death occurring in a mean of 15% to 20% of cases (range, 6%-76%).[2,5-8]

Multiple patient- and treatment-related risk factors for NSTI-associated mortality have been described, including patient age, comorbidities, cause of NSTI, extent of infection, microbiology of infection, time to antibiotic initiation, interhospital patient transfer, patient socioeco-

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nomic factors, admitting service (surgical vs nonsurgical), and location of treatment (community vs tertiary center).[2,6-17] Of all factors studied, only early diagnosis and definitive surgical treatment with aggressive debridement have consistently been shown to influence patient outcomes, including NSTI-associated mortality,[6,7,12,15,18] and are potentially modifiable.

The clinical presentation of NSTI can be variable, and most physicians' lifetime experience with NSTI is limited,[6] making early recognition and early surgical debridement challenging. Numerous studies have evaluated the usefulness of laboratory and imaging tests for diagnosing NSTI. Laboratory markers, such as hematocrit, white blood cell (WBC) count, and levels of serum sodium, bicarbonate, glucose, lactate, and hemoglobin,[9,11,12,14,19] have been inconsistently reported to be prognostic for NSTI-associated mortality. In 2004, the Laboratory Risk Indicator for Necrotizing Fasciitis score was developed as a tool for diagnosing necrotizing fasciitis.[16] The 6 components of this score include WBC count and levels of glucose, sodium, hemoglobin, serum creatinine, and C-reactive protein. Others propose using computed tomography[20] and computed tomography–based scoring systems[19] to aid in diagnosing NSTI. Despite recent advancements in our understanding of NSTI, early recognition and diagnosis of NSTI remain challenging.

Given the limited experience of any single institution and the relative rarity of NSTI, the prior work studying prognosis, risk factors, and NSTI-associated outcomes have generally examined all-comers with NSTI. The effects of common comorbidities, such as smoking, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, and heart disease and coronary artery disease on NSTI-associated outcomes have been studied. However, immunocompromised patients are a minor subset of those included in prior retrospective studies of NSTI. In 2010, a study[8] using the National Surgical Quality Improvement Program registry identified 668 cases of NSTI; less than 10% of the patients were immunocompromised, and these were poorly characterized. On univariate analysis, both malignancy and treatment with corticosteroids were associated with NSTI-related mortality. On multivariate analysis, malignancy remained a significant predictor of mortality. There is otherwise a scarcity of research on immunocompromised patients with NSTI. The aim of this study was to evaluate the effect of immunocompromised status on the clinical presentation of NSTI, time to recognition/diagnosis and treatment of NSTI, and NSTI-associated outcomes.

METHODS

PATIENTS

Our institution (Brigham and Women's Hospital and Dana-Farber Cancer Institute) is a tertiary academic hospital and cancer center in Boston, Massachusetts. Following institutional review board approval, we performed a retrospective review of all patients 18 years or older diagnosed as having been treated for NSTI at our institution between November 25, 1995, and April 25, 2011. In total, 201 patients were identified. Forty-six patients were immunocompromised, as defined by the presence of 1 or more of the following: active malignancy, diagnosis of human immunodeficiency virus or AIDS, corticosteroid treatment (prednisone [10 mg] or equivalent), receipt of chemotherapy or radiation therapy at the time of presentation, or prior solid organ or bone marrow transplantation with receipt of chronic immunosuppression. We performed extensive individual medical record reviews from the time of presentation to our institution until follow-up loss or death. Mortality data were ascertained in February 2012 from the Social Security Death Index.

Demographic data collected include patient sex, age at presentation, body mass index (calculated as weight in kilograms divided by height in meters squared), medical comorbidities, and American Society of Anesthesiologists physical status class. We obtained variables pertaining to the initial presentation (vital signs, NSTI location and cause, physical examination findings, laboratory test values at presentation, vasopressor or inotropic requirement, mode of admission to our institution, time between the onset of symptoms and presentation, time to diagnosis after presentation, and time to and extent of first surgical debridement), as well as factors related to NSTI treatment (intraoperative findings, the number of surgical debridements, and time to initiation of appropriate antibiotic therapy). Radiological, intraoperative frozen section, and permanent pathology and microbiology reports were reviewed. Outcome data, including the date of death and the discharge location, were obtained. The primary outcome of interest was NSTI-associated in-hospital mortality.

STATISTICAL ANALYSIS

Basic descriptive statistics were calculated for categorical variables (frequency and percentage) and continuous variables (median [interquartile range]). Discrete data were analyzed using a Fisher exact comparison, and continuous data were analyzed using a *t* test. Univariate analyses were performed to examine the association of candidate risk factors with the outcome of interest for all patients and for immunocompromised patients. Statistically significant variables from univariate analysis were retained in multivariate logistic regression analysis (full model). A reduced model was then created by applying stepwise selection to the set of candidate variables using significance levels of .30 and .35 to allow a variable into the model and to stay in the model, respectively. For significant predictors that remained after selection in the final model, odds ratios (95% CIs) were estimated. The Hosmer-Lemeshow goodness-of-fit test was performed to assess the overall fit for the multivariate logistic regression models. For each test, 2-sided $P < .05$ was considered statistically significant. Statistical analyses were performed using commercially available software (SAS, version 9.3; SAS Institute, Inc).

RESULTS

PATIENT CHARACTERISTICS

During the study period, 201 patients were diagnosed as having NSTI and treated at our institution. These included 92 women and 109 men, with a median age of 54.7 years and a median body mass index of 28.7. **Table 1** summarizes the clinicodemographic characteristics of the study population. Forty-six patients were immunocompromised, as previously defined. Thirty-three (71.7%) had active malignancy, with almost half (22 [47.8%]) receiving chemotherapy or radiation therapy, 18 (39.1%) using

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Table 1. Clinicodemographic Characteristics Among 201 Patients With NSTI

Variable	All Patients (N = 201)	Immunocompromised Patients (n = 46)	Immunocompetent Patients (n = 155)	*P* Value[a]
Sex, No. (%)				
Female	**92** (45.8)	18 (39.1)	74 (47.7)	.32
Male	**109** (54.2)	28 (60.9)	81 (52.3)	
Age, median (IQR), y	54.7 (43.0-67.0)	59.6 (45.5-72.3)	52.7 (42.8-63.8)	.15
Body mass index, median (IQR)	28.7 (24.4-34.8)	25.9 (23.1-30.3)	29.4 (25.2-37.5)	.003
Body temperature at presentation, median (IQR), °C	37.3 (36.5-38.2)	37.4 (36.6-38.2)	37.2 (36.4-38.2)	.54
Heart rate at presentation, median (IQR), beats/min	101 (88-120)	109 (89-124)	100 (87-117)	.12
Systolic blood pressure at presentation, median (IQR), mm Hg	111 (100-129)	105 (96-118)	112 (102-132)	.02
Physical examination findings, No. (%)				
Erythema	**192** (95.5)	43 (93.5)	149 (96.1)	.39
Crepitus	**26** (12.9)	4 (8.7)	22 (14.2)	.46
Fluctuance	**28** (13.9)	3 (6.5)	25 (16.1)	.14
Purulent drainage	**55** (27.4)	5 (10.9)	50 (32.3)	.004
Necrosis	**81** (40.3)	15 (32.6)	66 (42.6)	.23
Bullae	**33** (16.4)	9 (19.6)	24 (15.5)	.51
American Society of Anesthesiologists physical status class, No. (%)				
I	**4** (2.0)	1 (2.2)	3 (1.9)	.07
II	**27** (13.4)	3 (6.5)	24 (15.5)	
III	**97** (48.3)	20 (43.5)	77 (49.7)	
IV	**47** (23.4)	11 (23.9)	36 (23.2)	
V	**11** (5.5)	6 (13.0)	5 (3.2)	
Unknown	**15** (7.5)	5 (10.9)	10 (6.5)	
Comorbidity, No. (%)				
Diabetes mellitus	**71** (35.3)	9 (19.6)	62 (40.0)	.01
End-stage renal disease	**10** (5.0)	4 (8.7)	6 (3.9)	.24
Liver disease	**8** (4.0)	4 (8.7)	4 (2.6)	.08
Coronary artery disease	**29** (14.4)	8 (17.4)	21 (13.5)	.48
Peripheral vascular disease	**8** (4.0)	0	8 (5.2)	.20

Abbreviations: IQR, interquartile range; NSTI, necrotizing soft-tissue infection.
[a] Comparing immunocompetent and immunocompromised patients.

corticosteroids, 10 (21.7%) taking a nonsteroidal immunosuppressant, and 2 (4.3%) having human immunodeficiency virus or AIDS. Five patients (10.9%) had undergone solid organ or bone marrow transplantation. Few had comorbidities described in previous studies[8,9,12,14,18] or other patient populations as risk factors for NSTI, including diabetes mellitus, cardiac disease, and liver disease.

At presentation, most patients were afebrile. Although the median systolic blood pressure at presentation was 111 mm Hg, 66 patients (32.8%) required vasopressor or inotropic support. The NSTI commonly involved the lower extremities (54.3%), perineum (40.3%), and trunk (36.8%). Patients were initially seen with erythema (95.5%), necrosis (40.3%), purulent drainage (27.4%), bullae (16.4%), fluctuance (13.9%), and crepitus (12.9%). The cause of NSTI was often unknown (89 patients [44.3%]) but was attributed to recent surgical or other invasive procedures in 30 patients (14.9%), trauma in 23 patients (11.4%), perianal or perirectal abscess in 17 patients (8.5%), and chronic wound in 12 patients (6.0%). Uncommon causes of NSTI included perforated viscus in 7 patients (3.5%), subcutaneous medication injection in 6 patients (3.0%), and intravenous drug use in 3 patients (1.5%).

Compared with immunocompetent patients, immunocompromised patients had lower body mass index (25.9 vs 29.4, $P = .003$) and lower systolic blood pressure (105 vs 112 mm Hg, $P = .02$) and were less likely to initially be seen with purulent drainage (10.9% vs 32.3%, $P = .004$). Immunocompromised patients with NSTI were less likely to have diabetes mellitus (19.6% vs 40.0%, $P = .01$).

LABORATORY TEST FINDINGS AND IMAGING AT PRESENTATION

Table 2 summarizes admission laboratory test results, including variables previously reported to be prognostic of NSTI-associated outcomes, such as serum calcium and lactate levels and the Laboratory Risk Indicator for Necrotizing Fasciitis score components (WBC count and levels of glucose, sodium, hemoglobin, serum creatinine, and C-reactive protein). Compared with immunocompetent patients, immunocompromised patients had lower WBC count, glucose level, hematocrit, and platelet count. They also had greater base deficit, lactate level, and creatinine level, although these differences did not reach statistical significance.

Imaging was obtained in 141 patients (70.1%), with computed tomography the most common modality used

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Table 2. Admission Laboratory Values Among 201 Patients With NSTI

Variable	Median (IQR)			*P* Value[a]
	All Patients (N = 201)	Immunocompromised Patients (n = 46)	Immunocompetent Patients (n = 155)	
LRINEC variables				
Serum sodium level, mEq/L	134 (131 to 138)	135 (132 to 137)	134 (130 to 137)	.42
Glucose level, mg/dL	132 (102 to 216)	124 (99 to 170)	134 (103 to 231)	.03
Creatinine level, mg/dL	1.3 (0.8 to 2.2)	1.5 (0.8 to 2.6)	1.2 (0.8 to 2.1)	.80
C-reactive protein level, mg/L	155 (74 to 255)	124 (33 to 194)	159 (86 to 265)	.12
White blood cell count, /μL	15 500 (9000 to 20 600)	6600 (1300 to 15 000)	17 200 (11 800 to 21 700)	<.001
Hematocrit, %	33.2 (29.6 to 37.7)	31.7 (27.8 to 35.2)	33.9 (30.2 to 38.7)	.003
pH	7.35 (7.27 to 7.41)	7.40 (7.29 to 7.40)	7.30 (7.27 to 7.41)	.45
Base deficit, mEq/L	−3 (8 to 0)	−5 (−7 to −1)	−3 (−8 to 0)	.65
Lactate level, mg/dL	16.2 (9.9 to 32.4)	21.6 (13.5 to 55.0)	14.4 (9.9 to 26.1)	.24
Anion gap, mEq/L	12 (9 to 15)	12 (9 to 15)	12 (9 to 16)	.96
Calcium level, mg/dL	8.2 (7.4 to 8.9)	8.0 (7.3 to 8.6)	8.3 (7.4 to 9.0)	.07
Albumin level, g/dL	2.7 (2.2 to 3.2)	2.9 (2.2 to 3.4)	2.7 (2.1 to 3.2)	.82
Bands, %	8 (3 to 18)	11 (3 to 23)	8 (3 to 16)	.32
Platelet count, $\times 10^3$/μL	248 (149 to 364)	133 (60 to 254)	271 (184 to 403)	<.001
International normalized ratio	1.3 (1.2 to 1.6)	1.4 (1.2 to 1.9)	1.3 (1.2 to 1.6)	.59
Erythrocyte sedimentation rate, mm/h	74 (42 to 97)	42 (38 to 44)	81 (61 to 104)	.03

Abbreviations: IQR, interquartile range; LRINEC, Laboratory Risk Indicator for Necrotizing Fasciitis; NSTI, necrotizing soft-tissue infection.

SI conversion factors: To convert sodium level to millimoles per liter, multiply by 1.0; glucose level to millimoles per liter, multiply by 0.0555; creatinine level to micromoles per liter, multiply by 88.4; C-reactive protein level to nanomoles per liter, multiply by 9.524; white blood cell count to $\times 10^9$/L, multiply by 0.001; hematocrit to proportion of 1.0, multiply by 0.01; base deficit to millimoles per liter, multiply by 1.0; lactate level to millimoles per liter, multiply by 0.111; anion gap to millimoles per liter, multiply by 1.0; calcium level to millimoles per liter, multiply by 0.25; albumin level to grams per liter, multiply by 10; platelet count to $\times 10^9$/L, multiply by 1.0.

[a] Comparing immunocompetent and immunocompromised patients.

(78.7%) followed by radiography (19.1%), ultrasonography (7.1%), and magnetic resonance imaging (6.4%). Among 141 patients who underwent imaging at initial evaluation, gas was seen in 50.4%.

TIME TO DIAGNOSIS AND FIRST TREATMENT

Time to diagnosis after presentation and time to initiation of antibiotics were similar for immunocompetent and immunocompromised patients with NSTI (**Table 3**). Appropriate antibiotic therapy was initiated at presentation in 93.5% of patients in both groups. However, compared with immunocompetent patients, the way in which immunocompromised patients were initially seen at our institution and were managed on arrival differed significantly. Immunocompromised patients were more frequently seen directly at our institution instead of undergoing interhospital transfer. They were also more frequently admitted to medical services than to surgical services. Diagnosis of NSTI and first surgical debridement were delayed in immunocompromised patients compared with immunocompetent patients ($P < .001$ and $P = .001$, respectively).

Few immunocompromised patients compared with immunocompetent patients underwent immediate surgical debridement on admission (4.3% vs 61.3%, $P = .001$). Rather, at the time of NSTI presentation, immunocompromised patients were hospitalized inpatients (32.6%) or were first admitted to inpatient wards (32.6%) or intensive care units (30.4%) before the first surgical debridement. No debridement was pursued in 15.2% of immunocompromised patients vs in 0.6% of immunocompetent patients.

MICROBIOLOGY FINDINGS

Wound cultures were obtained at the time of admission or at the first surgical debridement in 191 patients (95.0%) and were polymicrobial in 58.7%. Anaerobes, gram-negative rods, β-hemolytic streptococcal species, coagulase-negative *Staphylococcus* species, *Enterococcus* species, and *Staphylococcus aureus* were the most commonly cultured pathogens in both patient groups. Wound cultures were positive for diphtheroids in 21 patients, all from the immunocompromised group ($P < .001$ compared with the immunocompetent group). Peripheral blood cultures were obtained at admission in 187 patients (93.0%). More immunocompromised patients compared with immunocompetent patients had positive blood cultures within 24 hours of admission (41.3% vs 20.0%, $P = .006$).

SURGICAL TREATMENT AND OUTCOMES

The median number of surgical debridements among all patients was 3; immunocompromised patients underwent a median of 2 surgical debridements ($P < .001$ compared with the immunocompetent patients) (Table 3). The median length of hospitalization was 15 days for all patients and was similar for immunocompetent patients and immunocompromised patients (**Table 4**). Overall, NSTI-associated in-hospital mortality was high but was

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Table 3. Evaluation and Treatment Variables Among 201 Patients With NSTI

Variable	No. (%)			*P* Value[a]
	All Patients (N = 201)	Immunocompromised Patients (n = 46)	Immunocompetent Patients (n = 155)	
Initial presentation				
BWH/DFCI	**107** (53.2)	34 (73.9)	73 (47.1)	.001
Referring hospital	**94** (46.8)	12 (26.1)	82 (52.9)	
Admitting service				
Medical	**51** (25.4)	25 (54.3)	26 (16.8)	<.001
Surgical	**150** (74.6)	21 (45.7)	129 (83.2)	
Mode of admission				
Floor	**32** (15.9)	15 (32.6)	17 (11.0)	.001
Intensive care unit	**54** (26.9)	14 (30.4)	40 (25.8)	
Operating room	**97** (48.3)	2 (4.3)	95 (61.3)	
Inpatient	**18** (9.0)	15 (32.6)	3 (1.9)	
Time from onset of symptoms to first presentation, h				
<12	**19** (9.5)	7 (15.2)	12 (7.7)	.15
12-24	**30** (14.9)	9 (19.6)	21 (13.5)	
>24	**142** (70.6)	28 (60.9)	114 (73.5)	
Unknown	**10** (5.0)	2 (4.3)	8 (5.2)	
Time from presentation to diagnosis, h				
<12	**125** (62.2)	22 (47.8)	103 (66.5)	<.001
12-24	**35** (17.4)	18 (39.1)	17 (11.0)	
>24	**38** (18.9)	6 (13.0)	32 (20.6)	
Unknown	**3** (1.5)	0	3 (1.9)	
Time from presentation to first surgical procedure, h				
<12	**118** (58.7)	17 (37.0)	101 (65.2)	.001
12-24	**35** (17.4)	15 (32.6)	20 (12.9)	
>24	**37** (18.4)	7 (15.2)	30 (19.4)	
No surgery	**8** (4.0)	7 (15.2)	1 (0.6)	
Unknown	**3** (1.5)	0	3 (1.9)	
Time from presentation to initiation of antibiotics, h				
<12	**169** (84.1)	37 (80.4)	132 (85.2)	.07
12-24	**12** (6.0)	6 (13.0)	6 (3.9)	
>24	**17** (8.5)	3 (6.5)	14 (9.0)	
Unknown	3 (1.5)	0	3 (1.9)	
No. of trips to the operating room[b]				
0	**8** (4.0)	7 (15.2)	1 (0.6)	<.001
1	**46** (22.9)	8 (17.4)	38 (24.5)	
2	**41** (20.4)	15 (32.6)	26 (16.8)	
3	**22** (10.9)	3 (6.5)	19 (12.3)	
4	**39** (19.4)	3 (6.5)	36 (23.2)	
>4	**45** (22.4)	10 (21.7)	35 (22.6)	

Abbreviations: BWH/DFCI, Brigham and Women's Hospital and Dana-Farber Cancer Institute; NSTI, necrotizing soft-tissue infection.
[a] Comparing immunocompetent and immunocompromised patients.
[b] The median (interquartile range) numbers of trips to the operating room were 3 (1-4) for all patients, 2 (1-4) for immunocompromised patients, and 3 (2-4) for immunocompetent patients.

significantly higher among immunocompromised patients compared with immunocompetent patients. Of 28 immunocompromised patients (60.9%) who survived hospitalization for NSTI, 2 were discharged to hospice.

We next sought to identify factors associated with NSTI-related in-hospital mortality among all patients and immunocompromised patients treated at our institution. Among all patients, various factors were associated with NSTI-related in-hospital mortality on univariate analysis (eTable 1; http://www.jamasurg.com). On multivariate analysis, the following remained statistically significant: the absence of intraoperative bleeding, lower albumin level and systolic blood pressure, and failure to initiate appropriate antibiotic therapy at presentation, as well as older age and higher international normalized ratio and American Society of Anesthesiologists physical status class (**Table 5**). The Hosmer-Lemeshow goodness-of-fit test indicates that the final model fits the data well ($P = .87$). Among 46 immunocompromised patients, multiple factors were similarly associated with NSTI-related in-hospital mortality on univariate analysis (eTable 2). Only vasopressor or inotropic requirement at presentation (β coefficient, 3.898; odds ratio, 49.318 [95% CI, 3.028-803.182]; $P = .006$) and

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Table 4. Outcomes Among 201 Patients With NSTI

Variable	All Patients (N = 201)	Immunocompromised Patients (n = 46)	Immunocompetent Patients (n = 155)	*P* Value[a]
Length of hospitalization, median (IQR), d	15 (8-27)	14 (3-26)	15 (9-28)	.72
Discharge location, No. (%)				
Home	**58** (28.9)	9 (19.6)	49 (31.6)	.01
Rehabilitation or skilled nursing facility	**93** (46.3)	17 (37.0)	76 (49.0)	
Death[b]	**48** (23.9)	18 (39.1)	30 (19.4)	
Hospice	**2** (1.0)	2 (4.3)	0	
Current status, No. (%)				
Alive	**103** (51.2)	11 (23.9)	92 (59.4)	.001
Dead	**98** (48.8)	35 (76.1)	63 (40.6)	

Abbreviations: IQR, interquartile range; NSTI, necrotizing soft-tissue infection.
[a] Comparing immunocompetent and immunocompromised patients.
[b] The cause of in-hospital mortality was sepsis in 48 patients.

Table 5. Multivariate Analysis of Clinicodemographic and Treatment Factors and NSTI-Associated In-Hospital Mortality Among 201 Patients With NSTI

Variable	*P* Value	β Coefficient	Odds Ratio (95% CI)
Systolic blood pressure	.03	−0.034	0.967 (0.938-0.997)
Albumin level	.02	−0.549	0.578 (0.368-0.906)
International normalized ratio	.02	0.612	1.844 (1.086-3.133)
Age	.002	0.069	1.072 (1.026-1.120)
American Society of Anesthesiologists physical status class	.005	1.160	3.190 (1.433-7.098)
Absence of bleeding during surgery	.001	2.150	8.582 (2.339-31.493)
Appropriate antibiotic therapy	.002	−3.726	0.024 (0.002-0.245)

Abbreviation: NSTI, necrotizing soft-tissue infection.

fewer surgical debridements (β coefficient, −1.949; odds ratio, 0.142 [95% CI, 0.040-0.510]; *P* = .003) remained statistically significant on multivariate analysis. The final model is also a good fit for the data (*P* = .89, Hosmer-Lemeshow goodness-of-fit test).

DISCUSSION

To our knowledge, this is the first study to examine NSTI in immunocompromised patients. We examined a cohort of 201 patients diagnosed with and treated for NSTI during a 15-year period at our institution. Forty-six patients were immunocompromised.

Despite considerable advancement in our knowledge, diagnostics, and treatment of the disease, NSTIs are severe infections associated with high mortality rates (15%-50%).[6] The diagnosis of NSTI can be challenging, and it can be difficult to distinguish NSTI from other soft-tissue infections. Although rare, with 500 to 1500 cases reported in the United States annually, the incidence of NSTI is increasing.[4,6,17]

We found that overall NSTI-associated in-hospital mortality in this study was 23.9% but was markedly higher in immunocompromised patients compared with immunocompetent patients (39.1% vs 19.4%, *P* = .01). Not unexpectedly, immunocompromised patients differed from immunocompetent patients in several clinicodemographic characteristics. However, our study revealed striking differences in how immunocompromised patients initially seen with NSTI were evaluated, triaged, and treated compared with immunocompetent patients, potentially affecting NSTI-associated outcomes.

Prior studies[16,17] report that admission laboratory values might assist in diagnosing NSTI and predicting NSTI-associated mortality. The previously mentioned Laboratory Risk Indicator for Necrotizing Fasciitis score is calculated using factors found to be independently predictive of necrotizing fasciitis.[16] More recently, admission WBC count exceeding 15 400 /μL and serum sodium level of less than 135 mEq/L have been proposed to aid in the early diagnosis of NSTI,[11] while lower serum sodium and higher lactate levels on admission have been associated with increased mortality (to convert WBC count to $\times 10^9$/L, multiply by 0.001; to convert sodium level to millimoles per liter, multiply by 1.0).[17]

Clinical suspicion and diagnosis of NSTI may often be based not only on physical examination but also on laboratory findings described in the literature (hyponatremia, leukocytosis, and elevated lactate and C-reactive protein levels). In the present study, hyponatremia was associated with NSTI in immunocompromised and immunocompetent patients (median serum sodium level among all patients, 134 mmol/L), consistent with prior studies.[11,16,17] However, only immunocompetent patients with NSTI demonstrated a leukocytosis response to NSTI. Contrary to the Laboratory Risk Indicator for Necrotizing Fasciitis model, in which higher

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WBC count was associated with NSTI-associated mortality, in our study immunocompromised patients compared with immunocompetent patients had lower WBC counts at presentation (6600/μL vs 17 200/μL, $P < .001$) but higher in-hospital mortality. Immunocompromised patients may be unable to mount the typical response to serious infection secondary to their underlying condition or treatments for such conditions and may fail to manifest typical signs and symptoms of NSTI, such as fever and leukocytosis.

Interhospital transfer has also been reported to be a prognostic factor for NSTI-related in-hospital mortality. Using the National Surgical Quality Improvement Program registry, one study[8] reported that interhospital transfer correlated with increased NSTI-related mortality, while direct admission was associated with reduced mortality among all-comers with NSTI. Similarly, using the Nationwide Inpatient Sample, another study[6] recently reported an association between interhospital transfer and increased risk of in-hospital mortality after surgical therapy for necrotizing fasciitis. Although neither study examined the relationship between interhospital transfer and time to first surgical therapy, it is proposed and conceivable, if not likely, that interhospital transfer may contribute to delay in surgical debridement, potentially leading to increased mortality. Indeed, the prognostic factor most consistently shown to be associated with worse NSTI-related morbidity and mortality is longer time to first surgical debridement.[9,12,15,17,18,21] In a study[12] of 198 patients, the mean times from admission to first debridement were 1.2 days among survivors of NSTI and 3.1 days among nonsurvivors ($P = .005$), while another study[7] of 65 patients with NSTI reported mean times from admission to first operation of 25 hours in survivors and 90 hours in nonsurvivors ($P < .001$). Other investigators recently found that a delay in surgical treatment of more than 12 hours was associated with an increased number of surgical debridements and with higher incidences of septic shock and acute renal failure.[15]

It is concerning that NSTI may not have been considered in the differential diagnosis or recognized as early as it might have been among immunocompromised patients in this study, possibly delaying surgical debridement and contributing to the higher NSTI-associated in-hospital mortality seen in this group. Indeed, we found that, although immunocompromised patients were more likely to initially be seen directly at our institution and were less likely to undergo interhospital transfer compared with immunocompetent patients, NSTI diagnosis and initial surgical treatment were delayed. On admission, immunocompromised patients were also more likely to be admitted to medical services rather than to surgical services and were less likely to undergo definitive surgical debridement on admission, possibly reflecting underrecognition of NSTI in this vulnerable patient population at the time of presentation.

There are several limitations of this study, including the retrospective nature of the analysis, the setting of a single large institution, and the modest sample size. This study was conducted at a hospital affiliated with a major cancer institution, possibly contributing to our patient cohort having more advanced malignant disease and, in rare cases, being on the last line of treatment, potentially contributing to higher-than-expected NSTI-associated in-hospital mortality compared with other study populations. Although the use of large multicenter databases to address clinical questions has proven advantages, our study of this unique patient subgroup benefits from meticulous data compilation, individual medical record review, and data verification that would be prohibitive using a regional or national database.

In conclusion, immunocompromised patients have delays in NSTI diagnosis and early surgical treatment and have higher NSTI-associated in-hospital mortality compared with their immunocompetent counterparts. They may initially be seen with NSTI atypically, making the diagnosis challenging for the evaluating physician. Therefore, it would be prudent for those caring for this vulnerable patient population to maintain a heightened level of suspicion for NSTI and to consider early surgical evaluation. Further studies are needed to improve our understanding of NSTI in immunocompromised patients and outcomes in this patient population.

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Correspondence: Reza Askari, MD, Department of Surgery, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (raskari@partners.org).
Author Contributions: *Study concept and design:* Keung, Adams, and Askari. *Acquisition of data:* Keung, Nuzhad, and Adams. *Analysis and interpretation of data:* Keung, Liu, Adams, Ashley, and Askari. *Drafting of the manuscript:* Keung, Liu, Nuzhad, Adams, and Askari. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Keung and Liu. *Administrative, technical, and material support:* Nuzhad, Adams, and Ashley. *Study supervision:* Adams, Ashley, and Askari.
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