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ORIGINAL SCIENTIFIC REPORT

Factors Associated with Mortality and Amputation Caused by Necrotizing Soft Tissue Infections of the Upper Extremity: A Retrospective Cohort Study

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Abstract

Background It is unclear what the exact short-term outcomes of necrotizing soft tissue infections (NSTIs), also known and necrotizing fasciitis of the upper extremity, are and whether these are comparable to other anatomical regions. Therefore, the aim of this study is to assess factors associated with mortality within 30-days and amputation in patients with upper extremity NSTIs.

Methods A retrospective study over a 20-year time period of all patients treated for NSTIs of the upper extremity was carried out. The primary outcomes were the 30-day mortality rate and the amputation rate in patients admitted to the hospital for upper extremity NSTIs.

Results Within 20 years, 122 patients with NSTIs of the upper extremity were identified. Thirteen patients (11%) died and 17 patients (14%) underwent amputation. Independent risk factors for mortality were an American Society of Anesthesiologists (ASA) classification of 3 or higher (OR 9.26, 95% CI 1.64–52.31) and a base deficit of 3 meq/L or greater (OR 10.53, 95% CI 1.14–96.98). The independent risk factor for amputation was a NSTI of the non-dominant arm (OR 3.78, 95% CI 1.07–13.35). Length of hospital stay was 15 (IQR 9–21) days.

Conclusion Upper extremity NSTIs have a relatively low mortality rate, but a relatively high amputation rate compared to studies assessing NSTIs of all anatomical regions. ASA classification and base deficit at admission predict the prognosis of patients with upper extremity NSTIs, while a NSTI of the non-dominant side is a risk factor for limb loss.

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Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body mass index
CI	Confidence interval
ICD	International classification of diseases
ICU	Intensive care unit
IVIG	Intravenous immunoglobulins
IQR	Interquartile range
GAS	Group A beta-hemolytic streptococcus
LRINEC	Laboratory Risk Indicator for Necrotizing Fasciitis
NSTI	Necrotizing soft tissue infection
OR	Odds ratio
RPDR	Research Patient Data Registry
TBSA	Total body surface area
SD	Standard deviation

Introduction

Necrotizing soft tissue infections (NSTIs) are rapidly spreading and progressive infection of the soft tissues, most often affecting the fascia and subcutaneous layers [1–3].

The extremities have been described to be affected in 45–74% of all NSTI cases, of which the lower extremity are most commonly involved [2, 4, 5]. NSTIs of the upper extremity have reported frequencies varying between 7 and 27% [6–8]. Most of the studies assessing upper extremity NSTIs are limited to small case series or big national database studies with less detail about the presentation and admission itself [6–8]. Due to this low representation of upper extremity NSTIs in the literature, it is unknown what the exact short-term outcomes are and whether they are comparable to NSTIs affecting other anatomical regions. Knowledge of risk factors for mortality and morbidity provides insight into the prognosis and possibilities to improve outcomes of NSTIs of the upper extremity.

Therefore, this study aims to assess which factors are associated with mortality within 30 days and amputation in patients with necrotizing soft tissue infections of the upper extremity.

Methods

This study was approved by the hospitals' institutional review board. A retrospective study of patients treated for NSTIs of the upper extremity at two academic referral centers between January 1998 and January 2018 was carried out. We identified eligible patients from the institution's Research Patient Data Registry (RPDR) by using the International Classification of Diseases (ICD)-9 (928.86) and ICD-10 (M72.6) codes for necrotizing fasciitis. The search resulted in 1507 patients. All patients diagnosed with NSTIs of the upper extremity were eligible for inclusion and determined the sample size. Since no pathognomonic clinical symptoms are known for NSTIs, the diagnosis needed to be established either by histopathology or by microbiology (e.g., gram stain and/or definitive culture) [1, 9, 10]. Cases in which the disease started at another anatomical region but progressed to one or both upper extremities were included as well. Exclusion criteria were patients <18 years and pregnancy at time of the infection.

Outcome measures and explanatory variables

The primary goals of this study were to describe the 30-day mortality rate and the amputation rate in patients with upper extremity NSTIs. In addition, we described the microbiology, types of procedures performed and hospital course.

The patient demographics extracted from medical charts include age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, comorbidities, medical history, smoking status, history of intravenous drug use and work status. The extracted disease-related characteristics include time from symptoms to diagnosis, affected side, dominant hand, causative event for the NSTI, date of causative event, location where symptoms started, affected body areas, parts of upper extremity affected by the NSTI, vital signs and laboratory results at presentation and causative microorganism found. The extracted treatment-related variables include the hospital of first debridement, amputation, mortality, date of death, intensive care unit (ICU) admittance, length of ICU and hospital stay, type and number of surgeries performed for the NSTI, date of last surgery for the NSTI, infectious complications during admission and discharge location. If the ASA classification was unknown, the researchers determined the ASA classification based on comorbidities known prior to the NSTI. We defined manual laborers as workers mainly doing physical work dominated by grasping and lifting [11]. The extent of the NSTI was approximated by calculating the percentage of total body surface area (TBSA) affected using the rule of nines commonly used in burns [12]. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was calculated if the necessary laboratory results were available. The LRINEC score is used to predict the likelihood of NSTIs. A LRINEC score <6 represents a low suspicion for NSTI [13]. By using the definitive culture results, we classified the NSTIs in type I (polymicrobial), type II (monomicrobial) or type

III (e.g., *Clostridium* spp., *Vibrio* spp. or gram-negative bacteria) [14].

Statistical analysis

Continuous parametric variables are presented as means with standard deviations (SDs), continuous nonparametric variables as medians with interquartile ranges (IQRs) and categorical variables as frequencies with percentages. Missing data were handled using pairwise deletion. Univariable logistic regressions were used to identify predictors for mortality and amputation. Variables with a p value <0.10 were eligible for inclusion in the multivariable logistic regression with simultaneous entry followed by backward selection. Only the most clinically relevant variables were selected to prevent overfitting the model, and variables with small numbers of occurrence in our cohort (e.g., 6 patients with a specific variable) were not included due to their limited statistical power. For analyses related to surgical procedures, the Mann–Whitney U test was used. For all analyses, a p value of <0.05 was considered statistically significant. Analyses were performed with STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

After exclusion, 122 eligible patients were identified with a mean age of 50 ± 17 years (Fig. 1). Patients were predominately classified ASA classification 1 or 2 (n = 74, 62%), which is indicative for no or minor comorbidities. The forearm was involved in most patients (n = 89, 74%). If a causative event was known, an injection was most frequently described (n = 26, 35%), of which 21 cases were caused by self-administrated intravenous drugs (Tables 1, 2).

Mortality within 30 days

Thirteen patients (11%) died within 30 days after the NSTI diagnosis. Nine of these patients (83%) were classified as ASA 3 or 4, indicating severe and/or multiple comorbidities. Patients with fatal NSTIs died at a median of 3 days after hospital admission (IQR 1–8), with the most common cause of death being sepsis (n = 10, 77%) (Table 3). In three other patients (23%), further surgical treatment was averted due to patients' wishes combined with severe preexisting comorbidities.

Univariable analyses showed that higher age (OR 1.07, 95% CI 1.03–1.12), ASA classification 3 or 4 compared to ASA 1 or 2 (OR 9.00, 95% CI 1.85–43.85), history of intravenous drug use (OR 4.04, 95% CI 1.07–15.50), a higher respiratory rate (OR 1.10, 95% CI 1.00–1.21), a higher glucose (OR 1.00, 95% CI 1.00–1.02), a higher base deficit (OR 1.40, 95% CI 1.14–1.72) or a higher serum lactate at time of diagnosis (OR 1.65, 95% CI 1.17–2.32), NSTIs that started at another anatomical region than the upper extremity (OR 10.60, 95% BI 1.89–21.76), NSTIs at other anatomical regions (especially the trunk and lower extremity) besides the upper extremity (OR 6.33, 95% CI 1.84–21.76), NSTIs affecting a greater TBSA (OR 1.05, 95% CI 1.00–1.10) and NSTIs of the shoulder (OR 3.87, 95% CI 1.10–13.61) resulted in a significantly greater risk at dying of the NSTI (Tables 1, 2, 3).

Multivariable analysis showed that an ASA classification of 3 or higher (OR 9.26, 95% CI 1.64–52.31) and a base deficit of 3 meq/L or greater (OR 10.53, 95% CI

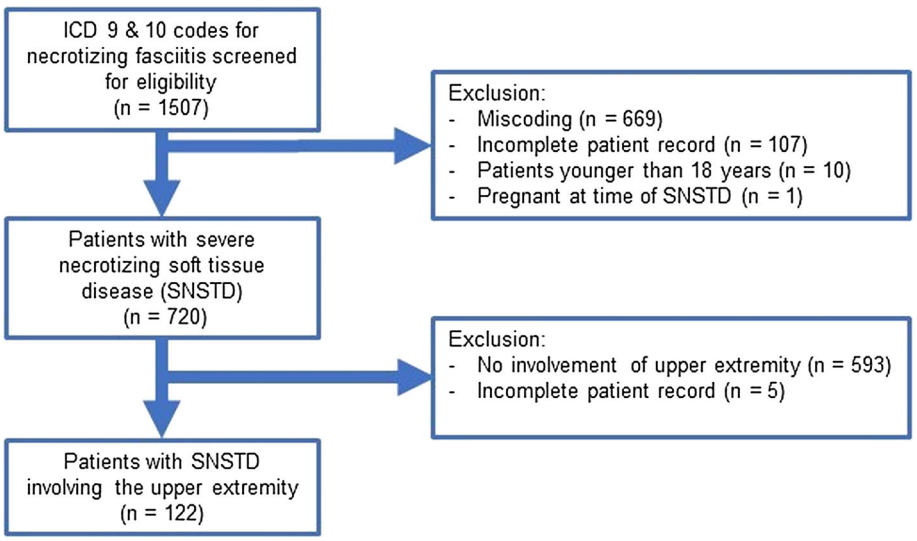

Fig. 1 Flowchart of patient inclusion and exclusion of necrotizing soft tissue infections of the upper extremity

Table 1 Patient characteristics associated with mortality and amputation in patients with necrotizing soft tissue infections of the upper extremity

	Total	Died ≤30 days	Survived	OR	Amputation	Limb salvage	OR
	n = 122 (100%)	*n* = 13 (11%)	*n* = 109 (89%)	(95% CI)	*n* = 17 (14%)	*n* = 105 (86%)	(95% CI)
Age in years, mean ± SD	50 ± 17	67 ± 14	48 ± 17	**1.07 (1.03–1.12)**	52 ± 20	50 ± 17	1.01 (0.98–1.04)
Sex, *n* (%)							
Female	53 (43)	3 (6)	50 (94)	0.35 (0.09–1.36)	7 (13)	46 (87)	0.90 (0.32–2.54)
Male	69 (57)	10 (14)	56 (86)	2.82 (0.74–10.83)	10 (14)	59 (86)	1.11 (0.39–3.15)
Body mass index in kg/m^2[a], median (IQR)	25 (23–31)	26 (23–32)	25 (23–31)	1.03 (0.95–1.13)	27 (25–34)	25 (23–30)	1.01 (0.92–1.10)
ASA classification[b], *n* (%)							
1 and 2	74 (62)	2 (3)	72 (97)	RC	9 (12)	65 (88)	RC
3 and 4	45 (38)	9 (20)	36 (80)	**9.00 (1.85–43.85)**	7 (16)	38 (84)	1.33 (0.46–3.86)
Diabetes mellitus, *n* (%)	20 (16)	4 (20)	16 (80)	2.58 (0.71–9.40)	4 (20)	16 (80)	1.71 (0.49–5.92)
History of malignancy[c], *n* (%)	16 (13)	4 (25)	12 (75)	**4.04 (1.07–15.50)**	4 (25)	12 (75)	2.36 (0.66–8.42)
Current smoker[d], *n* (%)	42 (35)	3 (7)	39 (93)	0.66 (0.17–2.65)	6 (14)	36 (86)	1.11 (0.38–3.32)
History of intravenous drug use[c], *n* (%)	35 (29)	2 (6)	33 (94)	0.41 (0.08–1.97)	2 (6)	33 (94)	0.29 (0.06–1.33)
Occupation at time of onset NSTI[d], *n* (%)							
Manual laborer	19 (17)	0 (0)	19 (100)	NC	1 (5)	18 (95)	0.29 (0.04–2.36)
Occupation without manual labor	44 (39)	3 (7)	41 (93)	0.77 (0.18–3.24)	6 (14)	38 (86)	0.93 (0.31–2.77)
Retired or unemployed	50 (44)	6 (12)	44 (88)	2.73 (0.65–11.50)	9 (18)	41 (82)	1.76 (0.60–5.10)
Vital signs at presentation, median (IQR)							
Systolic blood pressure in mmHg[e]	116 (102–132)	110 (96–132)	117 (102–133)	0.99 (0.97–1.02)	118 (110–146)	116 (101–128)	1.01 (0.99–1.04)
Diastolic blood pressure in mmHg[e]	65 (56–76)	65 (54–75)	65 (56–77)	0.98 (0.94–1.03)	74 (63–84)	65 (56–75)	**1.05 (1.00–1.09)**
Mean arterial pressure in mmHg[e]	82 (73–93)	83 (69–89)	82 (73–94)	0.99 (0.95–1.03)	92 (79–98)	81 (73–92)	1.03 (0.99–1.07)
Heart rate in beats per minute[e]	98 (87–116)	105 (99–125)	98 (86–111)	1.03 (0.99–1.06)	104 (97–120)	98 (87–115)	1.02 (0.99–1.05)
Respiratory rate in breaths per minute[f]	18 (16–20)	20 (20–30)	18 (16–20)	**1.10 (1.00–1.21)**	16 (16–20)	18 (16–20)	0.96 (0.84–1.09)
Laboratory results at presentation, median (IQR)							
C-reactive protein mg/L (reference: <10)[g]	145 (101–237)	140 (118–210)	146 (101–237)	1.00 (0.99–1.01)	155 (127–188)	144 (101–243)	0.99 (0.99–1.01)
White blood cell count × 10,000/μL (reference: 4–10)[h]	15 (9–22)	9 (4–18)	15 (9–23)	0.94 (0.88–1.01)	19 (7–34)	15 (9–22)	1.02 (0.99–1.06)
Hemoglobin in g/dL (reference ♀ 7.4–9.6; ♂ 8.6–10.7)[i]	11.2 (9.9–12.6)	11.0 (9.1–13.1)	11.2 (9.9–12.5)	0.88 (0.66–1.18)	10.3 (9.1–12.9)	11.3 (10.0–12.6)	0.81 (0.62–1.05)

Table 1 continued

	Total *n* = 122 (100%)	Died ≤30 days *n* = 13 (11%)	Survived *n* = 109 (89%)	OR (95% CI)	Amputation *n* = 17 (14%)	Limb salvage *n* = 105 (86%)	OR (95% CI)
Sodium in mmol/L (reference 136–146)[j]	135 (132–138)	137 (135–141)	135 (132–138)	1.14 (0.99–1.32)	135 (131–136)	135 (132–138_	0.96 (0.85–1.08)
Creatinine in mg/dL (reference ♀ 58–103; ♂ 74–120)[k]	1.0 (0.8–1.5)	1.6 (1.1–2.3)	1.0 (0.8–1.4)	1.39 (0.90–2.15)	1.2 (0.8–2.1)	1.0 (0.8–1.5)	1.07 (0.67–1.74)
Glucose in mg/dL (reference 3.6–5.6)[l]	119 (95–147)	145 (102–226)	118 (95–145)	**1.00 (1.00–1.02)**	115 (92–193)	120 (98–147)	1.00 (0.99–1.01)
Base deficit in meq/L (reference: − 3–3)[m]	4.3 (0.7–8)	11.0 (6.3–13.3)	3.2 (-0.1–7.0)	**1.40 (1.14–1.72)**	5.0 (-0.5–9.7)	4.0 (1.4–8.1)	1.00 (0.89–1.11)
Serum lactate in mmol/L (reference: 0.5–1.0)[n]	1.7 (1.2–3.0)	4.5 (2.4–14.3)	1.7 (1.1–2.5)	**1.65 (1.17–2.32)**	2.7 (1.3–5.9)	1.7 (1.2–3.0)	1.12 (0.95–1.31)
LRINEC score at presentation[o], median (IQR)	4 (2–8)	4 (2–7)	5 (2–8)	0.91 (0.67–1.23)	7 (3–10)	4 (2–7)	1.22 (0.90–1.66)

Odds ratios in bold are statistically significant

ASA American Society of Anesthesiologists; *CI* confidence interval; *IQR* interquartile range; *OR* odds ratio; *NC* not calculable; *NSTI* necrotizing soft tissue infection; *RC* reference; *SD* standard deviation

Missing cases: [a]20 missing; [b]3 missing; [c]1 missing; [d]9 missing; [e]21 missing; [f]30 missing; [g]72 missing; [h]12 missing; [i]13 missing; [j]58 missing; [k]49 missing; [l]49 missing; [o]70 missing

1.14–96.98) are both independent risk factors for mortality (Table 4).

Amputation

Seventeen patients (14%) underwent amputation in an attempt to gain control of the infection, which was either an amputation during the index surgery ($n = 9$) or performed secondarily ($n = 8$). Three patients underwent amputation but died eventually. Types of amputation were an amputation of digit(s) ($n = 7$, 41%), transradial ($n = 2$, 12%), transhumeral ($n = 6$, 35%) or forequarter amputation ($n = 2$, 12%).

Univariable analyses assessing the risk at amputation showed that only NSTIs of the non-dominant side (OR 3.79, 95% CI 1.09–13.16), a higher diastolic blood pressure at presentation (OR 1.05, 95% CI 1.00–1.09) and NSTIs of the hand (OR 5.04; 95% CI 1.37–18.58) had a greater risk at undergoing amputation (Tables 1, 2, 3).

Multivariable analysis showed that NSTIs of the non-dominant side (OR 3.78, 95% CI 1.07–13.35) were an independent risk factor for amputation (Table 4).

Microbiology

NSTIs of the upper extremity were predominately classified as type II ($n = 75$, $n = 70$%), of which a Group A beta-hemolytic Streptococcus (GAS) was most commonly isolated ($n = 48$, 64%). Of these patients, 10 patients (21%) received intravenous immunoglobulins (IVIG). Administration of IVIG was not associated with reduced mortality or amputation rates. Furthermore, 22 patients (20%) had type I NSTIs and 11 patients (10%) had type III NSTIs. Subgroup analysis of the specific isolated microorganisms found no relation between the isolated microorganisms and 30-day mortality or risk at amputation (Table 2 and Appendix 1).

Hospital course

Eighty patients (66%) first presented to an outside hospital; 63 of these patients (79%) were transferred to one of the two academic centers before their first debridement was performed. Transferring patients before the initial debridement did not result in higher mortality or amputation rates (OR 0.38, 95% CI 0.11–1.30 and OR 1.40, 95% CI 0.50–3.96, respectively) (Table 2).

Median length of hospital stay was 15 days (IQR 9–21). Eighty-six patients were admitted to ICU (70%) for a median stay of 3 days (IQR 2–9). During the hospital stay, 71 patients (58%) developed infectious complications (e.g., toxic shock syndrome, sepsis, pneumonia). After hospital discharge, patients were discharged home ($n = 63$, 68%),

Table 2 Disease characteristics associated with mortality and amputation in patients with necrotizing soft tissue infections of the upper extremity

	Total *n* = 122 (100%)	Died ≤30 days *n* = 13 (11%)	Survived *n* = 109 (89%)	OR (95% CI)	Amputation *n* = 17 (14%)	Limb salvage *n* = 105 (86%)	OR (95% CI)
Time from onset symptoms to diagnosis in days[a], median (IQR)	2 (1–4)	1 (1–2)	2 (1–4)	0.70 (0.47–1.03)	1 (0–3)	2 (1–4)	0.93 (0.77–1.11)
Transfer without first debridement at presenting hospital, *n* (%)	63 (52)	4 (6)	59 (94)	0.38 (0.11–1.30)	10 (16)	53 (84)	1.40 (0.50–3.96)
Affected side, *n* (%)							
Left	62 (51)	6 (10)	56 (90)	0.81 (0.26–2.57)	11 (18)	51 (82)	1.94 (0.66–5.64)
Right	56 (46)	7 (12.5)	49 (87.5)	1.43 (0.45–4.53)	5 (9)	51 (91)	0.44 (0.15–1.34)
Bilateral	4 (3)	0 (0)	4 (100)	NC	1 (25)	3 (75)	2.13 (0.21–21.70)
Dominant hand affected[b], *n* (%)	51 (55)	1 (2)	50 (98)	0.39 (0.03–4.46)	4 (8)	47 (92)	**0.26 (0.08–0.92)**
Causative event if known[c], *n* (%)							
Injection (IVDU, blood drawl)	26 (35)	1 (4)	25 (96)	0.28 (0.03–2.26)	2 (8)	24 (92)	0.45 (0.09–2.11)
Trauma without open wound	14 (19)	3 (21)	11 (79)	0.37 (0.05–3.02)	4 (29)	10 (71)	2.32 (0.72–7.48)
Traumatic wound	21 (28)	1 (5)	20 (95)	2.43 (0.58–10.06)	5 (24)	16 (76)	2.63 (0.73–9.48)
Bite (bug/cat/human)	10 (13)	0 (0)	10 (100)	NC	1 (10)	9 (90)	0.76 (0.09–6.47)
Prior surgery	4 (5)	1 (25)	3 (75)	2.94 (0.28–30.58)	2 (50)	2 (50)	6.87 (0.90–52.46)
Days between causative moment and diagnosis[d], median (IQR)	4 (3–8)	5 (4–7)	4 (3–8)	0.97 (0.80–1.17)	6 (4–10)	4 (3–6)	1.04 (0.95–1.14)
Infection not starting at the upper extremity, *n* (%)	6 (5)	3 (50)	3 (50)	**10.60 (1.89–59.59)**	0 (0)	6 (100)	NC
Other body regions affected by NSTI, *n* (%)	19 (16)	6 (32)	13 (68)	**6.33 (1.84–21.76)**	1 (5)	18 (95)	0.30 (0.04–2.43)
Head/neck involved	2 (2)	0 (0)	2 (100)	NC	0 (0)	2 (100)	NC
Trunk involved	17 (14)	5 (29)	12 (71)	**5.05 (1.42–17.96)**	1 (6)	16 (94)	0.35 (0.04–2.81)
Perineum involved	1 (1)	1 (100)	0 (0)	NC	0 (0)	1 (100)	NC
Lower extremity involved	6 (5)	3 (50)	3 (50)	**10.50 (1.87–59.03)**	0 (0)	6 (100)	NC
Percentage of total body surface area (TBSA) affect by NSTI, median (IQR)	4 (3–6)	6 (3–15)	4 (3–6)	**1.05 (1.00–1.10)**	5 (3–6)	4 (3–6)	0.98 (0.92–1.06)
Type of NSTI based on definitive cultures[e], *n* (%)							
Type I	22 (20)	2 (9)	20 (91)	0.84 (0.17–4.22)	3 (14)	19 (86)	0.87 (0.23–3.38)
Type II	75 (70)	7 (9)	68 (91)	0.72 (0.20–2.66)	11 (15)	64 (85)	0.93 (0.29–2.93)
Type III	11 (10)	2 (18)	9 (82)	2.17 (0.41–11.64)	2 (18)	9 (82)	1.32 (0.26–6.75)
Levels of upper extremity involved[a], *n* (%)							
Hand	64 (53)	5 (8)	59 (92)	0.61 (0.18–2.03)	14 (22)	50 (78)	**5.04 (1.37–18.58)**

Table 2 continued

	Total *n* = 122 (100%)	Died ≤30 days *n* = 13 (11%)	Survived *n* = 109 (89%)	OR (95% CI)	Amputation *n* = 17 (14%)	Limb salvage *n* = 105 (86%)	OR (95% CI)
Forearm	89 (74)	6 (7)	83 (93)	0.31 (0.09–1.06)	15 (17)	74 (83)	3.04 (0.65–14.1)
Upper arm	63 (52)	7 (11)	56 (89)	1.33 (0.40–4.43)	8 (13)	55 (87)	0.79 (0.28–2.21)
Shoulder	23 (18)	5 (23)	17 (77)	**3.87 (1.10–13.61)**	2 (9)	20 (91)	0.56 (0.12–2.65)
Number of upper extremity levels involved[a], median (IQR)	2 (1–2)	2 (1–3)	2 (1–2)	0.91 (0.42–1.96)	2 (2–3)	2 (1–2)	1.78 (0.95–3.32)
Most proximal level of upper extremity involved[c], *n* (%)							
Hand	12 (10)	2 (17)	10 (83)	RC	2 (17)	10 (83)	RC
Forearm	42 (35)	2 (5)	40 (95)	0.25 (0.03–2.00)	7 (17)	35 (83)	1.00 (0.17–5.59)
Upper arm	45 (37)	3 (7)	42 (93)	0.36 (0.05–2.43)	6 (13)	39 (87)	0.77 (0.13–4.40)
Shoulder	22 (18)	5 (23)	17 (77)	1.47 (0.24–9.04)	2 (9)	20 (91)	0.50 (0.06–4.09)

Odds ratios in bold are statistically significant

CI Confidence interval; *IQR* interquartile range; *IVDU* intravenous drug use; *NC* not calculable; *NSTI* necrotizing soft tissue infection; *OR* odds ratio; *RC* reference; *TBSA* total body surface area

Missing cases: [a]1 missing; [b]30 missing; [c]47 missing; [d]11 missing; [e]13 missing

to a rehabilitation facility (*n* = 39, 36%) or transferred to another hospital for further care (*n* = 1, 1%) (Table 3).

Patients underwent a median of four operations (IQR 3–6, range 0–22). A median of three debridement procedures (IQR 2–4, range 0–10) and a median of one reconstructive procedure (IQR 1–2, range 0–9) were performed. The first attempt at wound closure was made a median of 8 days (IQR 4–12) after diagnosis. Closure of debridement wounds in surviving patients without amputations was done by using skin grafts (*n* = 50, 54%), delayed primary closure with sutures (*n* = 25, 27%), flap surgery (*n* = 9, 10%) and flap surgery combined with skin grafts (*n* = 8, 9%). There was no difference in number of surgeries between patients requiring amputation for infection control and those with salvaged upper extremities (Appendix 2).

Discussion

The 30-day mortality rate of 11% found in this study is low compared to mortality rates previously described for NSTIs [2, 3, 15, 16]. Over 20 years ago, a cumulative mortality rate of 34% was described [17]. Looking at studies for the past ten years, the mortality rate of NSTIs varies between 6% and 33% [2, 3, 15, 16]. The mortality rate probably decreased due to improvement in awareness and treatment, both in surgical care and in critical care support [9]. The cumulative mortality rate described for upper extremity NSTIs is 18.3% (90 patients died out of 493 included patients in 8 studies), with rates as low as 9% and as high as 36% [6, 18–24]. The low mortality rate in this study might be caused by the relatively large group of intravenous drug user and type II NSTIs. Both of these groups are known to consist of young patients with few comorbidities, which are two factors previously associated with lower mortality rates [25, 26]. The mortality rate for NSTIs of the extremity has been suggested to be lower compared to NSTIs of other anatomical regions (e.g., head, neck, trunk), since NSTIs at these location are commonly more widespread upon presentation and tend to be more difficult to treat [27].

Only two previous studies have looked at factors associated with mortality in upper extremity NSTIs. Both studies found that patients with preexisting comorbidities and patients presenting with septic symptoms had a greater risk of dying [20, 22]. In this study, the ASA classification was used to assess the overall physical status of the patients and the severity of the comorbidities combined. A higher ASA classification has been linked to higher mortality after major trauma and a wide variety of surgical procedures [28, 29]. Patients with upper extremity NSTIs and major or multiple comorbidities (ASA 3 or 4) had a nine times

Table 3 Disease outcomes and hospital course of patients with necrotizing soft tissue infections of the upper extremity

	Total *n* = 122 (100%)	Died ≤30 days *n* = 13 (11%)	Survived *n* = 108 (89%)	OR (95% CI)	Amputation *n* = 17 (14%)	Limb salvage *n* = 105 (86%)	OR (95% CI)
Amputation, *n* (%)	17 (14)	3 (18)	14 (82)	2.04 (0.50–8.31)	17 (100)	NA	NA
Digits	7 (41)	1 (14)	6 (86)		7 (100)	NA	
Forearm	2 (12)	0 (0)	2 (100)		2 (100)	NA	
Transhumeral	6 (35)	1 (17)	5 (83)		6 (100)	NA	
Forequarter	2 (12)	1 (50)	1 (50)		2 (100)	NA	
Mortality rate within 30 days, *n* (%)	13 (11)	13 (100)	NA	NA	3 (23)	10 (77)	2.04 (0.50–8.31)
Time between admission and death in days, median (IQR)	3 (1–8)	2 (1–4)	NA	NA	1 (1–18)	3 (2–8)	0.99 (0.92–1.06)
Length of hospital stay in days, median (IQR)	15 (9–21)	NA	15 (10–24)	NA	10 (6–19)	15 (9–21)	0.99 (0.96–1.02)
ICU admittance, *n* (%)	86 (70)	12 (14)	74 (86)	5.68 (0.71–45.40)	13 (15)	73 (85)	1.42 (0.43–4.71)
Length of ICU stay[a], median (IQR)	3 (2–9)	3 (1–7)	4 (2–9)	0.95 (0.85–1.07)	5 (3–11)	3 (2–8)	1.00 (0.96–1.03)
Infectious complications during hospital course, *n* (%)	73 (60)	13 (18)	60 (82)	NC	11 (15)	62 (85)	1.27 (0.44–3.70)
Sepsis/toxic shock syndrome	70 (57)	13 (19)	57 (81)	NC	10 (14)	60 (86)	1.07 (0.38–3.03)
Pneumonia	8 (7)	0 (0)	8 (100)	NC	2 (25)	6 (75)	2.20 (0.41–11.92)
Discharge location, *n* (%)				NA			
Home	68 (63)	NA	68 (100)		6 (9)	62 (91)	0.38 (0.13–1.10)
Rehabilitation facility	39 (36)	NA	39 (100)		8 (21)	31 (79)	2.12 (0.75–6.01)
Transfer to other hospital	1 (1)	NA	1 (100)		0 (0)	1 (100)	NC

Odds ratios in bold are statistically significant

CI Confidence interval; *ICU* intensive care unit; *IQR* interquartile range; *NA* not applicable; *NC* not calculable; *OR* odds ratio

Missing cases: [a]14 missing

greater risk of dying compared to patients with no to minimal comorbidities (ASA 1 or 2). This association has not yet been described for upper extremity NSTIs, but has been described by two studies assessing NSTIs of all body regions [2, 4, 30].

Base deficit at admission was also found to predict mortality due to upper extremity NSTIs. Patients with a base deficit ≥3 meq/L at admission had an 11-time greater risk at dying compared to patients with a base deficit of <3 meq/L. A base deficit provides a fast estimate of the physiological disturbance of the patient, is a marker for shock and is usually part of the standard diagnostic armamentarium in the emergency department [31, 32]. Base deficits are already used to predict complications and mortality in trauma and intensive care patients and has been described by Elliot et al. to also predict mortality in NSTI patients [31–34]. It has been suggested that the LRINEC score might also be predictive for mortality, since this score also looks at markers for sepsis severity in NSTI patients; however, in this study the LRINEC score was not predictive for mortality and was in most patients far below the cutoff point for NSTI suspicion [13, 35].

Amputation was in 14% of the cases required for management of the infection. Previously described amputation rates for NSTIs range from 6% to 28%, while the amputation rate of studies assessing the upper extremity varies between 6% and 36% with a cumulative amputation rate of 9% [19, 21–23, 34, 36–38]. This rate is lower than seen in our study, which might be related to the lower mortality rate. More patients survived, but the patients who survived

Table 4 Multivariable logistic regression of risk factors for mortality and amputation in patients with necrotizing soft tissue infections of the upper extremity

30-day mortality	OR (95% CI)	Standard error	*p* value
ASA classification ≥III	9.26 (1.64–52.31)	8.18	**0.012**
Base deficit ≥3 meq/L at time of diagnosis	10.53 (1.14–96.98)	11.93	**0.038**
Amputation	OR (95% CI)	Standard error	*p* value
Non-dominant side affected	3.78 (1.07–13.35)	2.43	**0.039**
Hand affected by NSTI	2.97 (0.75–11.82)	1.55	0.122

Variables utilized in multivariable logistic regression, but eliminated during backward regression:

30-day mortality analysis: age, ASA classification, history of malignancy, respiratory rate at presentation, base deficit at presentation, total body surface affected, other body regions affected by NSTI

Amputation analysis: diastolic blood pressure at presentation, dominant hand affected, hand involved

ASA American Society of Anesthesiologists; *CI* confidence interval; *NSTI* necrotizing soft tissue infection; *OR* odds ratio. P-values in bold are statistically significant

might have required more extreme measures, such as amputation, to survive. Only diabetes mellitus and sepsis have previously been associated with amputation in patients with NSTIs of the upper extremity [22]. This study did not find a relation between those factors but did find that patients with NSTIs of the non-dominant arm were more likely to undergo amputation. This seemed not to be influenced by a more distal location of the infection or by an injection, most commonly done in the non-dominant arm, as causative event. Therefore, we hypothesize that this might represent surgical bias. Surgeons might possibly be more likely to resort to amputation if the non-dominant arm was affected, weighing infection control and the remaining functionality of the dominant arm. Fortunately, due to improved awareness and diagnostics, the amputation rate has declined during the last 5 years of the study.

This study is limited by its retrospective nature. First, during the inclusion process patients might have been missed for inclusion due to miscoding of ICD codes or underdiagnosing of NSTIs in deceased patients. Second, the accuracy of retrospective data is determined by the accuracy of reporting of findings in patients' chart. This may have led to non-differential misclassification or absent variables. This was the case for the exact time (in hours) to diagnosis and surgery. Third, we included patients who first presented to outside hospitals, which results in less detailed information about findings at the initial presentation. Fourth, this study assesses a broad study period during which the management of critical ill patients changed as well. Our data are representative of actual practice including the management variations; however, these variations should be kept in mind. Finally, due to the rarity of NSTIs and the associated small sample sizes and limited occurrence of the outcomes, sparse data bias should be kept in mind during the interpretation of the results. However, the strength of this study is that this is one of the biggest and most detailed studies of NSTIs of the upper extremity.

Conclusion

NSTIs of the upper extremity have a relatively low mortality rate, but a relatively high amputation rate compared to studies assessing NSTIs of all anatomical regions. ASA classification and base deficit at admission can predict the prognosis of patients with upper extremity NSTIs, while a NSTI of the non-dominant arm is a risk factor for limb loss.

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Compliance with ethical standards

Conflict of interest Dr. Eberlin is a consultant for AxoGen and Integra. Dr. Chen received grants by Miami Device Solutions, OMeGA and Acumed. All authors declare to have no commercial relations that might pose a conflict of interest in connection with the manuscript.

Ethical approval This study was approved by the hospitals' institutional review board.

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