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Predicting necrotising soft tissue infections in people who inject drugs: poor performance of the Laboratory Risk Indicator for Necrotising Fasciitis score and development of a novel clinical predictive nomogram in a retrospective cohort with internal validation

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Introduction: Necrotising soft tissue infections (NSTI) can threaten life and limb. Early identification and urgent surgical debridement are key for improved outcomes. NSTI can be insidious. Scoring systems, like the Laboratory Risk Indicator for Necrotising Fasciitis (LRINEC), exist to aid diagnosis. People who inject drugs (PWID) are high risk for NSTI. This study aimed to assess the utility of the LRINEC in PWID with lower limb infections and develop a predictive nomogram.

Methods: A retrospective database of all hospital admissions due to limb-related complications secondary to injecting drug use between December 2011 and December 2020 was compiled through discharge codes and a prospectively maintained Vascular Surgery database. All lower limb infections were extracted from this database, dichotomised by NSTI and non-NSTI with the LRINEC applied. Specialty management times were evaluated. Statistical analyses involved: chi-square; Analysis of "variance"; Kaplan–Meier, and receiver operating characteristic curves. Nomograms were developed to facilitate diagnosis and predict survival.

Results: There were 557 admissions for 378 patients, with 124 (22.3%; 111 patients) NSTI. Time from admission to: theatre and computed tomography imaging respectively varied significantly between specialties ($P = 0.001$). Surgical specialties were faster than medical ($P = 0.001$). Vascular surgery received the most admissions and had the quickest time to theatre. During follow-up there were 79 (20.9%) deaths: 27 (24.3%) NSTI and 52 (19.5%) non-NSTI. LRINEC ≥ 6 had a positive predictive value of 33.3% and sensitivity of 74% for NSTI. LRINEC <6 had a negative predictive value of 90.7% and specificity of 63.2% for non-NSTI. Area under the curve was 0.697 (95% CI: 0.615–0.778). Nomogram models found age, C-reactive protein, and non-linear albumin to be significant predictors of NSTI, with age, white cell count, sodium, creatinine, C-reactive protein, and albumin being significant in predicting survival on discharge.

Conclusion: There was reduced performance of the LRINEC in this PWID cohort. Diagnosis may be enhanced through use of this predictive nomogram.

Keywords: injecting drug use, intravenous drug use, Laboratory Risk Indicator for Necrotising Fasciitis, necrotising fasciitis, necrotising soft tissue infections, nomogram, people who inject drugs, prediction model substance use

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Introduction

Necrotising soft tissue infections (NSTI) represent a clinically aggressive group of infections characterised by rapidly progressive soft tissue destruction with high rates of morbidity and mortality[1,2]. Early recognition, imaging and prompt surgical debridement have been associated with improved survival[3]. Studies demonstrate that patients managed by clinicians familiar with the clinical course of NSTI have better survival rates[3,4].

An increasing incidence of NSTI has been highlighted by observational cohort studies, with rising rates of NSTI among PWID[4–7]. A 10-year review of deaths related to NSTI showed half of the deaths linked to NSTI involved PWID[6]. The UK has one of the highest rates of illicit drug use and related deaths in Europe[8]. Scotland claims the highest rate of drug deaths in Europe, and possibly the world, with the city of Dundee being at the epicentre of this drug deaths crisis[9,10]. In parallel to drug death rates, the number of UK hospital admissions for bacterial infections secondary to injecting drug use have been rising[8]. This increase in hospital admissions for skin and soft tissue infections has also been mirrored in the USA, who are also currently in the midst of a drug deaths epidemic[11–13]. The limb-related complications of injecting drug use can create a considerable surgical workload[14,15]. This is relevant worldwide with an estimated 15.6 million PWID globally[16,17]. Injecting of stimulant drugs is also rising across Europe and the USA, with potential for increased frequency of injecting (shorter half-lives and riskier behaviour patterns), injury and infection[8,13,18]. Local evidence suggests that the burden of managing these complex patients with NSTI secondary to injecting drug use falls to vascular surgery[14,15].

NSTI remain a diagnostic challenge, as the early features are often indistinguishable from non-necrotising infections, especially within the PWID population[1,2]. Scoring systems to facilitate clinicians in diagnosing NSTI have been developed. One such tool that is commonly described is the LRINEC, which uses C-reactive protein (CRP), white cell count (WCC), haemoglobin, sodium, creatinine and blood glucose levels[19]. Patients are scored over 6 domains with LRINEC scores of ≥ 6 being associated with the highest predictive values for NSTI[19]. However, there are concerns regarding the sensitivity of the LRINEC tool[20] and it has not yet been validated for specific use in a PWID population[19]. Within vascular surgery in Scotland there does not tend to be regular use of scoring systems to aid in diagnosing NSTI, perhaps as this surgical community is primed to have a high index of suspicion. Vascular surgery seem increasingly involved in the management of such cases, with previous work highlighting reduced recognition of NSTI in patients not admitted directly to vascular surgery[15].

This study primarily aimed to assess the utility of the LRINEC score within a population of PWID with infective lower limb complications and devise an intuitive, predictive nomogram model as a further, more specific adjunct for discerning the likelihood of NSTI within this cohort. It also aimed to develop a further nomogram to aid in prognosticating on survival among these patients following discharge from critical care and hospital, as well as evaluate time intervals for the management of patients within this cohort by specialty (based upon time from admission to computed tomography [CT] imaging and theatre, and CT imaging to theatre).

HIGHLIGHTS

- Necrotising soft tissue infections (NSTI) are diagnostically difficult with high-tariff consequences.
- The Laboratory Risk Indicator for Necrotising Fasciitis (LRINEC) score performed poorly at predicting NSTI in people who inject drugs (PWID).
- Surgical specialties were quicker at detecting NSTI than medical specialties.
- Vascular surgery managed most PWID NSTI and had the quickest management times.
- Predictive nomograms may aid diagnosis and prognostication within this cohort.

Methods

Population and database design

A retrospective database of all hospital admissions to a tertiary hospital due to limb-related complications secondary to injecting drug use between 1 December 2011 and 31 December 2020 was compiled. This healthboard is situated in a region with a high prevalence of problem drug use and related deaths. Patients were identified through multiple sources to enhance case capture. These sources included: the healthboard Business Unit using discharge codes (Appendix A, Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A328); a prospectively maintained vascular surgery unit operative database and the healthboard theatre management system (Centricity Opera Theatre Management System). The electronic records of all patients identified were interrogated for further relevant admissions perhaps eluding capture through the other sources, acknowledging the tendency for recurrent admissions within this cohort. This included patients undergoing surgery and those managed medically. All admissions identified were scrutinised and inclusion into the database documented up to two of the following examples of limb-related complications for each admission: groin and other limb abscesses; infected arterial pseudoaneurysms; NSTI; cellulitis; deep venous thromboses (DVTs); infected DVTs; limb ischaemia (from intra-arterial injecting, prior ligation, or mixed aetiology ulceration) or complications of venous insufficiency (e.g. diagnosis 1: infected arterial pseudoaneurysm; diagnosis 2: infected DVT). The presence or absence of NSTI was recorded for all cases. This study defined NSTI as infections which may involve any or all (multiple) fascial layers, extending from superficial (dermal, subcutaneous) to deep (musculature), characterised by friable fascia and rapid tissue destruction (necrosis)[2,21]. This allowed multiple relevant pathologies to be recorded.

Data for each admission were collected from patient records and cross-checked with imaging and operation notes. Data collected included: demographics; admission episode details (admitting specialty, in-hospital referral from admitting team to another in-hospital specialty for management, for NSTI patients: time from admission to theatre; time from admission to CT imaging and time from CT imaging to theatre); imaging modality; haematological and biochemical parameters at initial admission (haemoglobin, WCC, creatinine, CRP, D-Dimer, sodium, albumin, urea, lactate and creatinine kinase); microbiology (from pus/tissue cultures and blood cultures); presence of infective

endocarditis; blood-borne virus (BBV) testing, results and history; operation; major limb amputation (transtibial, transfemoral, hip disarticulation); critical care requirement – high dependency unit (HDU – level 2 care) and ICU (level 3 care); length of admission and mortality, with follow-up until 16 September 2021 or death. The time-points used to assess the management of NSTI were selected as they were considered the most reliably recorded. Although NSTI is largely a clinical diagnosis, imaging can act as an adjunct and so CT imaging was used as a fixed time-point to infer recognition of NSTI. CT features associated with NSTI include fascial involvement, non-enhancement of fascia, oedema extending across fascial planes and into muscle, as well as gas[22]. Critical care use and length of admission were used as surrogate markers for case complexity and morbidity. Caldicott Guardian approval was secured for accessing and storing patient data.

All admission episodes with an infective lower limb complication secondary to injecting drug use were extracted from this main database. These were primarily: groin and other limb abscesses; infected arterial pseudoaneurysms; presence or absence of NSTI; cellulitis and infected DVTs. These admissions were already dichotomised into NSTI and non-NSTI. The LRINEC score was applied to all admission episodes dependent upon the availability of the required parameters at initial presentation[19]. Admission episodes related to upper limb complications were excluded because of low numbers.

During the study period all patients presenting with signs of limb-related sepsis secondary to injecting drug use were commenced on empirical, broad-spectrum antibiotics covering gram negative, gram positive, and anaerobic organisms until microbiology cultures allowed for rationalisation, as per local healthboard guidelines. This included an anti-toxin, such as clindamycin, if there was suspicion of NSTI or evidence of septic shock.

This study has also been reported in accordance with the Strengthening The Reporting Of Cohort, Cross-sectional, and Case-control Studies in Surgery (STROCSS) criteria[23] (Appendix A, STROCSS guideline, Supplemental Digital Content 1, http://links.lww.com/JS9/A327). It has also been registered on the Research Registry with the according Unique Identifying Number (UIN): researchregistry8204[24].

Database statistical analyses

Descriptive statistics were reported using mean and range or median and interquartile range (IQR) depending on the spread of data. For comparisons of patients falling into different categories, the chi-square, independent *t*-test, Mann–Whitney, and one-way analysis of variance (ANOVA) were used as appropriate. Survival analysis was performed using Kaplan–Meier plot and log-rank statistic, with P-value < 0.05 denoting significance. A LRINEC score < 6 was taken to indicate an intermediate to high risk of having a NSTI[19]. A receiver operating characteristic (ROC) curve was created to determine the discriminatory power of LRINEC in distinguishing NSTI from non-NSTI. Data were analysed using Statistical Package for the Social Sciences, version 18 (IBM Corp.).

Nomogram model development

Global and best-fit logistic regression models were built to estimate the odds of developing NSTI, as well as global and best-fit survival models (Cox proportional hazard regression analysis) of time to discharge from critical care and time to discharge from hospital. The full dataset of haematological and biochemical covariates were used, including those used to inform the LRINEC scoring tool, but excluded D-dimer and creatine kinase as insufficient data were available.

Models and nomograms were developed using the R packages 'ggplot2,' 'hmisc,' and 'rms.' The modelling strategy was based on that recommended by Harrell[25]. We hypothesised that continuous variables were nonlinear and pre-specified 3 cubic splines (knots) to continuous variables and 1 *df* to categorical data. We restricted the number of events per variable (EPV) in the model according to the equation EPV = events or outcomes/15.

Global models were built using all variables and noted the partial χ^2statistic for testing the association of each predictor with outcome adjusted for all other predictors and the number of *df* used. Best-fit reduced models considered the number of *df* that could be spent, and how they could be spent. For example, continuous variables that showed a linear relationship with outcome were restricted to 1 *df*. Predictors were ranked by plotting Akaike's Information Criterion (AIC) defined as $\chi^2 - 2$ *df*. Initial estimation of shrinkage (γ) needed used the formula $\gamma = [\chi^2 - p)/\chi^2]$. The model was also interpreted graphically. Models were validated using calibration and discrimination. Internal validation used the bootstrap (200 iterations) to incorporate all data.

The corrected calibration slope (0 – 1, with value closer to 1 indicating better calibration) was obtained using bootstrapping bias-corrected (overfitting – corrected) estimates of predicted versus observed values. To check proportional hazards assumptions, we examined scaled Schoenfeld residuals.

Assessment of model discrimination between low-risk and high-risk patients, used the coefficient of determination (R^2), Dxy and the bias-corrected *C*-index. R^2 is the proportion of the variation in the dependent variable that is predictable from the independent variable(s). The *C*-index represents the probability of concordance, *c*, between predicted and observed survival, and is equivalent to the ROC area under the curve (AUC). Concordance is defined as the proportion of all pairs of subjects whose survival time can be ordered such that the subject with the higher predicted survival is the one who survived longer with $c = 0.5$ for random predictions and $c = 1$ for a perfectly discriminating model. An AUC of 1 indicates perfect discriminatory power of the model, with an AUC of 0.5 demonstrating no discrimination, while an AUC of 0.7–0.8 is considered acceptable and an AUC of 0.6–07 being poor.

Dxy is the difference between concordance and discordance probabilities and related to the *C*-index by the equation Dxy = 2 ($c - 0.5$). Discrimination of the binary outcome, NSTI, used the Brier score, a quadratic scoring rule. A Brier score can take on any value between 0 and 1, with 0 being the best score achievable and 1 being the worst score achievable. The lower the Brier score, the more accurate the prediction(s).

Models were developed in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Initiative recommendations (Appendix A, Supplemental Digital Content 2, http://links.lww.com/JS9/A328)[26]. Although checklists such as that recommended by TRIPOD standardise reporting, clinicians find mathematical models difficult to conceptualise. Therefore, we drew nomograms, computational two-dimensional graphs developed from complex mathematical functions that can be readily interpreted.

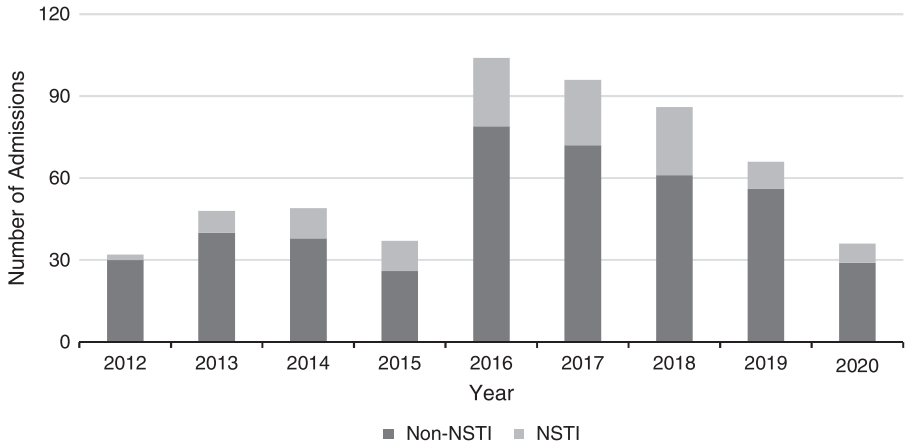


Figure 1. Admission numbers by year, dichotomised by necrotising soft tissue infection (NSTI) and non-NSTI (data for December 2011 is excluded no further data for the year 2011 was included).

Results

Admissions due to infective lower limb complications of injecting drugs

There were 557 admissions generated by 378 patients with infective lower limb complications secondary to injecting drug use, of which 330 (59.2%) admissions were male. The mean age was 38 ± 7.7 (range: 21–61) years. Of these 557 admissions, 124 (22.3%) were due to NSTI, representing 111 patients. Seventy-eight (62.9%) NSTI admissions were male. The mean age of admissions for those with NSTI was 40 ± 7.5, range: 24–58) years, compared with 37 ± 7.7, range: 21–61) years for non-NSTI ($P = 0.001$). Figure 1 displays the number of admissions per year (NSTI vs. non-NSTI). Table 1 characterises the NSTI and non-NSTI populations (age, sex, imaging modality, and diagnoses). The mean follow-up was 4.58 (median: 4.30) years.

Table 1

Admission demographics, imaging, and diagnoses

	NSTI	Non-NSTI	Total	*P*
Number of admissions (*n*)	124	433	557	–
Sex				
Male	78	252	330	0.347
Female	46	181	227	
Age (mean ± SD) (years)	40 ± 7.5	37 ± 7.7	38 ± 7.7	0.001
Imaging				
Ultrasound	18	138	156	0.001
CT	122	271	393	0.001
Diagnoses				
Groin abscess	76	224	300	0.060
Other abscess	5	28	33	0.311
Infected arterial pseudoaneurysm	37	44	81	0.001
Cellulitis	1	108	109	0.001
DVT	11	72	83	0.032
Infected DVT	3	55	58	0.001
Other	3	47	50	0.003

CT, computed tomography; DVT, deep venous thrombosis; NSTI, necrotising soft tissue infection.

Admitting specialty for necrotising soft tissue infection

Vascular surgery was the initial admitting specialty for 69 (55.7%) of these 124 NSTI admissions (Table 2). Onward referral to another specialty occurred in 52 (41.9%) of all NSTI cases, with 47 (90.4%) of these onward in-hospital referrals made to vascular surgery (Table 2). Overall, 116 (93.5%) NSTI admissions were ultimately under the care of vascular surgery for surgical management.

There was significant variation in time from admission to theatre (TTT) and time from admission to CT imaging (TAI) by admitting specialty ($P = 0.001$). The time from CT imaging to theatre (TIT) was not significantly different by admitting specialty ($P = 0.402$) (Table 3). Upon stratifying admitting specialties by surgical versus medical (Table 4), there was significant variation for TTT and TAI between surgical and medical specialties ($P = 0.001$), with no significant difference for time from CT imaging to theatre ($P = 0.652$). Only two NSTI cases did not have preoperative CT imaging (due to haemorrhage from an arterial pseudoaneurysm) and no NSTI cases were taken to theatre with only an ultrasound.

Table 2

Admission and referral by specialty

	n (%)		
Specialty team	Number of admissions	Number of onward in-hospital referrals received	Net total admissions
Vascular surgery	69 (55.7)	48 (92.3)	116 (93.5)
General surgery	20 (16.1)	1 (1.9)	3 (2.4)
Plastic surgery	1 (0.8)	3 (5.8)	3 (2.4)
Orthopaedics	5 (4.0)	0 (0)	1 (0.8)
Infectious disease	5 (4.0)	0 (0)[a]	1 (0.8)
Other medical[b]	24 (19.4)	0 (0)	0 (0)

[a]Following debridement one patient was referred to infectious diseases for continuing management of an infected DVT; another patient remained under infectious diseases with surgical debridement by the vascular surgery team.
[b]Other medical, acute medicine and general medicine.

Table 3

Time interval hours, by specialty, from admission through to theatre

	Mean (median, IQR) (h)		
Admitting specialty	**TTT**	**TAI**	**TIT**
Vascular surgery	10.8 (16.0, 5.0–21.0)	4.3 (13.6, 2.0–15.6)	7.5 (11.5, 4.5–16.8)
General surgery	36.0 (33.0, 18.8–51.8)	20.0 (13.3, 14.0–27.3)	22.0 (31.0, 10.0–41.0)
Plastic surgery	44.0 (–)[a]	20.5 (–)[a]	23.5 (–)[a]
Orthopaedics	21.0 (56.3, 10.8–67.0)	16.3 (38.3, 4.3–42.5)	18.0 (23.0, 8.3–31.3)
Infectious disease	80.0 (207.9, 17.5–225.4)	3.0 (171.5, 2.85–174.3)	19 (16.0, 11.35–27.3)
Other medical[b]	47.0 (54.0, 23.0–77.0)	22.3 (31.4, 13.55–44.8)	10.5 (23.0, 5.0–28.0)
P	0.001	0.001	0.402

[a]Note only one patient admitted under care of plastic surgery therefore no IQR.
[b]Other medical = acute medicine and general medicine.
IQR, interquartile range; TAI, time from admission to computed tomography imaging; TIT, time from computed tomography imaging to theatre; TTT, time from admission to theatre.

Length of stay and critical care use

Median length of hospital stay for the NSTI cohort was 14.5 (IQR: 22.3) days compared with 5 (IQR: 11.0) days for the non-NSTI group ($P = 0.001$). Of the 124 NSTI admissions, 43 (34.7%) required critical care. Thirty admissions needed the HDU, with a median length of HDU stay of 2 (IQR: 3) days, and 13 necessitated ICU admission, with a median length of ICU stay of 3 (IQR: 7) days. Among the 433 non-NSTI cohort, 28 (6.47%) required critical care, with 25 admissions to the HDU with a median HDU stay of 2 (IQR: 1) days and three required ICU, with a median ICU stay of 2 (IQR: –) days. Significantly more NSTI patients required both the HDU and ICU than non-NSTI ($P = 0.001$ for HDU and ICU, respectively).

Theatre, femoral vessel arterial ligation, and amputation

The mean number of trips to the operating theatre for debridement across all admissions was 1.54 (range: 1–7). Thirty-nine (31.5%) NSTI admissions underwent femoral vessel arterial ligation. Of these ligations, 28 were at the level of the common femoral artery, three at the external iliac artery, two at the superficial femoral artery, and two at the profunda femoris artery. The level of ligation in four patients was unclear from the data available. Sixteen (12.9%) patients underwent amputation, with two transtibial amputations, 10 transfemoral amputations and four hip disarticulations. Fifteen (93.8%) amputations were associated with arterial ligation.

In the non-NSTI group 49 patients required arterial ligation (11.3%). Of these ligations, 38 were at the common femoral artery, one external iliac artery, one superficial femoral artery, two profunda femoris artery and seven were unclear. There were five (1.15%) amputations (three, 0.69% subsequent to vessel ligation), with one transtibial, three transfemoral and one hip disarticulation. Three (60%) amputations were associated with arterial ligation.

Microbiology, bacteraemia, infective endocarditis, and blood-borne viruses

Forty-nine different species of bacteria were identified from the 557 admissions (pus and tissue cultures), with *Staphylococcus aureus* and mixed anaerobes being the commonest for both NSTI and non-NSTI cases (Table 5) (complete microbiology is displayed in Appendix A, Supplementary Tables 2 and 3, Supplemental Digital Content 2, http://links.lww.com/JS9/A328). There were 38 monomicrobial and 64 polymicrobial NSTI cases with 22 having no growth or no microbiology sent. There were 99 monomicrobial and 76 polymicrobial non-NSTI cases with 258 having no growth or no microbiology sent.

The rates of bacteraemia, infective endocarditis and BBV testing and history, dichotomised by NSTI and non-NSTI, are shown in Table 6. The complete microbiology for bacteraemia cases by NSTI and non-NSTI is documented in Appendix A (Supplementary Tables 4 and 5, Supplemental Digital Content 2, http://links.lww.com/JS9/A328). *Staphylococcus aureus* and *Enterococcus faecalis* were the most common species implicated in bacteraemia for both NSTI and non-NSTI (*Peptoniphilus harei* was joint second most frequent for non-NSTI).

Mortality and survival

Overall mortality, calculated from the index admission for the 378 patients, was 20.9% (79 deaths), with a mean survival of 8.4 (median survival: not reached) years. The NSTI group had a mortality of 24.3% (27 deaths), while the non-NSTI group had a mortality of 19.5% (52 deaths), with mean survival for NSTI and non-NSTI at 8.1 and 8.0 years, respectively (log-rank $P = 0.31$) (Fig. 2, median survival: not reached). In-hospital mortality was zero with one patient dying within 30 days of index admission (out-of-hospital, in the NSTI cohort).

Table 4

Time interval hours by medical or surgical group from admission through to theatre

	Mean (median, IQR) (h)		
Specialty group	**TTT**	**TAI**	**TIT**
Surgical	15.3 (25.9, 6.0–31.9)	6.8 (16.5, 2.0–18.5)	11.5 (16.1, 4.9–21.0)
Medical	47.0 (58.0, 23.0–81.0)	21.0 (38.8, 8.80–47.5)	11.0 (23.0, 5.00–28.0)
P	0.001	0.001	0.652

IQR, interquartile range; TAI, time from admission to computed tomography imaging; TIT, time from computed tomography imaging to theatre; TTT, time from admission to theatre.

Table 5

Top 10 bacterial organisms for NSTI and non-NSTI cases

Organism species	NSTI n (%)	Organism species	Non-NSTI n (%)
Staphylococcus aureus	47 (23.3)	*Staphylococcus aureus*	89 (32.2)
Mixed anaerobes	46 (22.8)	Mixed anaerobes	49 (17.8)
Streptococcus anginosus	11 (5.45)	*Enterococcus faecalis*	10 (3.62)
Enterococcus faecalis	7 (3.47)	*Staphylococcus epidermidis*	10 (3.62)
Escherichia coli	6 (2.97)	Group G streptococci	9 (3.26)
Group B streptococci	6 (2.97)	Group A streptococcus	8 (2.90)
Group C streptococci	6 (2.97)	Group B streptococci	7 (2.54)
Streptococcus mitis	6 (2.97)	Group C streptococci	7 (2.54)
Finegoldia magna	4 (1.98)	*Streptococcus anginosus*	7 (2.54)
Streptococcus oralis	4 (1.98)	*Streptococcus intermedius*	6 (2.17)
Total	202	Total	276

NSTI, necrotising soft tissue infection.

Haematological and biochemical parameters and Laboratory Risk Indicator for Necrotising Fasciitis prediction of necrotising soft tissue infection

Haematological and biochemical data from the 557 admission episodes were dichotomised into NSTI ($n=124$) or non-NSTI ($n=433$). Table 7 displays the biochemical parameters collected for each admission and variance between NSTI and non-NSTI.

The LRINEC scoring system was applied (CRP [mg/l], WCC [$\times 10^9$/l], haemoglobin [g/dl], sodium [mmol/l], creatinine [mmol/l], and glucose level [mg/l]) to all admissions with all pertinent parameters at presentation. LRINEC score calculation was possible for 251 (50 NSTI and 201 non-NSTI) cases.

Table 6

Presence of bacteraemia, infective endocarditis, blood-borne virus testing, and status

	n (%)		
	NSTI	Non-NSTI	Total
Bacteraemia			
Yes	23 (18.5)	77 (17.8)	100
No	53 (42.7)	141 (32.6)	194
Growth of uncertain significance	2 (1.61)	12 (2.77)	14
Blood cultures not taken	46 (37.1)	203 (46.9)	249
Infective endocarditis			
Yes	3 (2.42)	2 (0.46)	5
No	121 (97.6)	431 (99.5)	552
Blood-borne virus testing			
Yes	26 (21)	84 (19.4)	110
No	98 (79)	349 (80.6)	447
Blood-borne virus test results			
Hepatitis B	0 (0)	1 (1.19)	1
Hepatitis C	11 (42.3)	18[a] (21.4)	29
Hepatitis C – prior infection	2 (7.69)	12 (14.3)	14
HIV	0 (0)	1[b] (1.19)	1
History of hepatitis C			
Yes	75 (60.5)	258 (59.6)	333
No	49 (39.5)	175 (40.4)	224
Existing HIV diagnosis			
Yes	0 (0)	2 (0.46)	2
No	124 (100)	431 (99.5)	555

[a]One known hepatitis C receiving treatment.
[b]Known HIV infection receiving treatment.
NSTI, necrotising soft tissue infection.

A LRINEC ≥ 6 had a positive predictive value of 33.3%, with a sensitivity of 74% in identifying NSTI. A LRINEC <6 had a negative predictive value of 90.7%, with a specificity of 63.2% for identifying non-NSTI. Figure 3 demonstrates the ROC curve for the accuracy of the LRINEC score in distinguishing NSTI versus non-NSTI within this PWID cohort.

Nomogram models

Best-fit logistic models for predicting odds of NSTI and best-fit Cox proportionality survival models for time to discharge from hospital showed good calibration and discrimination, unlike the survival model for critical care (Table 8).

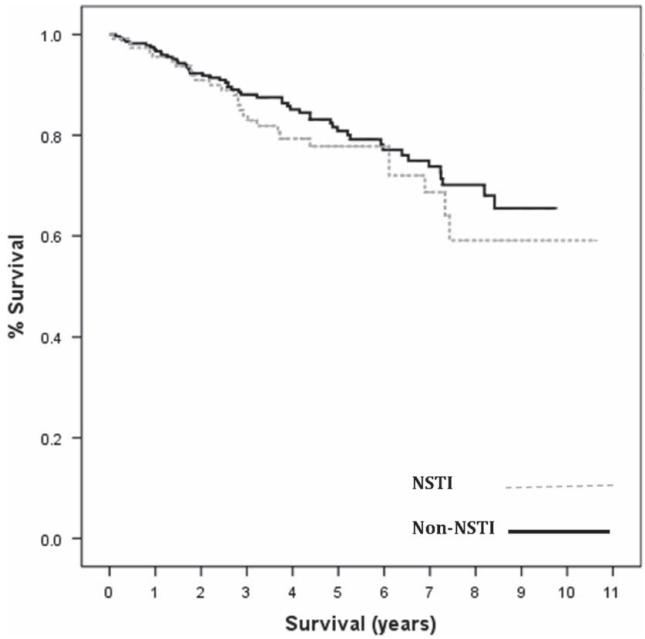
Tables of best-fit and global logistic models are shown in Appendix A (Supplementary Tables 6–8, Supplemental Digital Content 2, http://links.lww.com/JS9/A328). Continuous non-linear relationships and nomograms are shown in Figures 4A–F. Using our dataset, significant predictors of NSTI were age, CRP, and non-linear albumin. Survival on discharge from hospital was dependent on age, WCC, sodium, creatinine, CRP, and albumin.

Discussion

This study highlights the ongoing burden of pathology secondary to injecting drug use seen by clinicians within this region, with 557 admissions related to infective complications of the lower limb over a 9-year period. There can be reticence among PWID to seek medical attention, which can result in delayed, more advanced presentations, making management challenging and more resource intensive[27]. Microbial infections can transform into NSTI requiring radical surgical debridement, with 22.2% of infective admissions in this study found to have evidence of NSTI. Further, in this population, the LRINEC scoring tool was not sensitive enough to be used as an early warning system for recognition of NSTI.

We have previously reported vascular surgery to be particularly impacted by a high burden of limb-related complications secondary to injecting drug use[14,15]. This trend was also replicated in this study with 55.7% of NSTI cases admitted directly to vascular surgery, and following onward in-hospital referrals, vascular surgery ultimately managed 93.5% of these cases. The vast majority of PWID soft tissue sepsis was managed by vascular surgery. The UK surgical curriculums for general surgery, plastic surgery, trauma and orthopaedic surgery and vascular surgery have embedded the management of soft tissue sepsis and wound care within their curriculums. The UK Vascular Surgery Curriculum[28] ensures trainees have the requisite generic diagnostic and surgical skills in situations with or without any specific vascular injury. The same generic skills are curricular requirements of the other surgical specialties, however the burden of care was not equitable. With increasing subspecialisation, the experience in approaching perivascular soft tissue sepsis may become the domain of vascular surgery. This is important as vascular services are increasingly centralised in the UK[29], and vascular surgery teams are numerically smaller in terms of staffing and resources in comparison to other surgical specialties involved in the management of soft tissue sepsis.

There was significant variation between specialties in time from admission to theatre and CT imaging respectively, with the shortest times noted for patients admitted directly to vascular surgery. However, there was no significant variation between the specialties for the time from imaging to theatre. This suggests that



log-rank p=0.31

Number at Risk	0 years	1 years	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
NSTI	111	106	95	82	58	39	28	17	8	3	1
Non-NSTI	267	256	220	172	136	104	76	65	39	14	-

Figure 2. Kaplan–Meier survival curve by presence of necrotising soft tissue infections (NSTI).

Table 7

Blood parameters by presence NSTI versus non-NSTI

Blood parameter	NSTI/non-NSTI	Number of samples	Mean	SD	Range	*P*
D-Dimer (ng/ml)	NSTI	20	749.3	264.4	314–1279	0.273
	Non-NSTI	47	873.9	842.7	0–3501	
Haemoglobin (g/dl)	NSTI	121	109.4	22.0	80–152	0.001
	Non-NSTI	416	116.4	18.6	47–179	
White cell count ($\times 10^9$/l)	NSTI	122	14.8	6.5	3.8–36.4	< 0.001
	Non-NSTI	416	11.6	5.4	2.6–56.1	
CRP (mg/l)	NSTI	121	241.2	103.6	23–528	< 0.001
	Non-NSTI	421	148.3	100.2	3–432	
Sodium (mmol/l)	NSTI	119	134.0	3.6	122–145	< 0.001
	Non-NSTI	406	136.0	3.7	123–145	
Albumin (g/l)	NSTI	121	26.1	4.4	12–39.1	< 0.001
	Non-NSTI	414	30.9	5.6	4.4–45	
Urea (mmol/l)	NSTI	122	6.9	5.3	1.7–28.8	0.001
	Non-NSTI	425	5.2	3.7	1.8–44.0	
Creatinine (μmol/l)	NSTI	121	68.6	28.7	32–202	0.341
	Non-NSTI	417	64.8	25.6	23–279	
Lactate (mmol/l)	NSTI	77	1.7	1.2	0.5–7.4	0.012
	Non-NSTI	280	1.4	1.0	0.4–8.9	
Glucose (mg/l)	NSTI	53	7.2	3.7	5–28	< 0.001
	Non-NSTI	214	6.0	1.9	3–24	
Creatinine kinase (μ/l)	NSTI	14	383.5[a]	–	22–16 541	0.014
	Non-NSTI	37	74[a]	–	0–36 325	

[a]Median value reported.

CRP, C-reactive protein; NSTI, necrotising soft tissue infection.

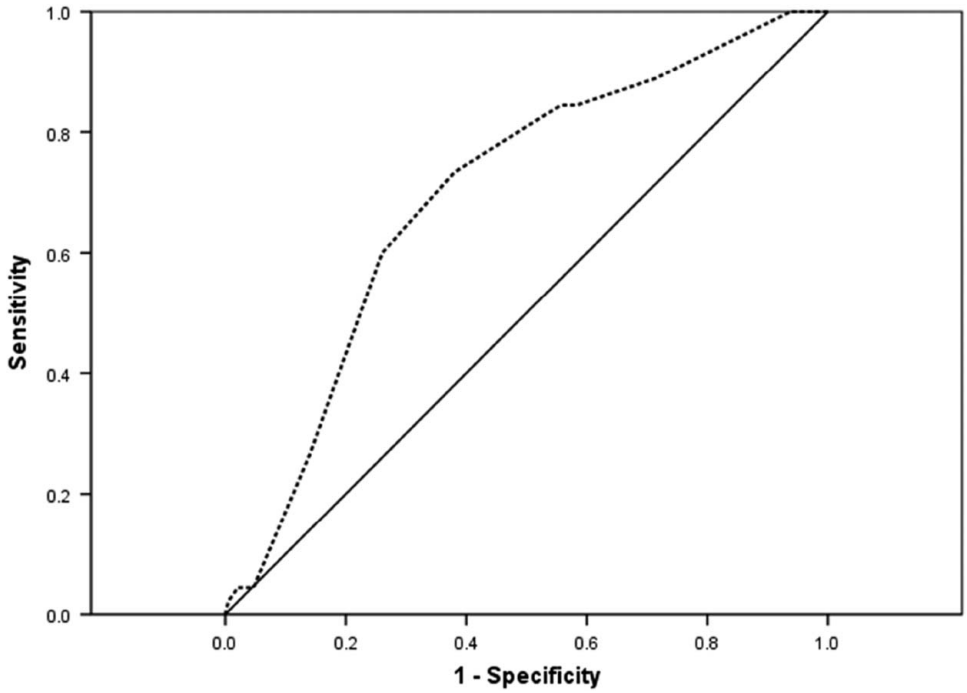


Figure 3. Receiver operating characteristic curve for Laboratory Risk Indicator for Necrotising Fasciitis score within our cohort, area under the curve = 0.697 (95% CI: 0.615–0.778).

once a diagnosis of NSTI is established all admitting teams instigated appropriate management and referral for debridement. Predictive scoring systems have been developed to aid in the early diagnosis of NSTI using haematological and biochemical measurements, clinical findings and physiological parameters[30–34]. The most cited scoring system for predicting NSTI is the LRINEC and multiple attempts to improve the accuracy of this tool have been reported[19,30–33]. Yoon and colleagues added magnetic resonance imaging to help identify NSTI. This study reported an improved sensitivity and predictive value when compared with the original LRINEC. However, no significant difference in specificity was demonstrated[30]. The use of magnetic resonance imaging in the emergency clinical setting poses challenges in the form of cost, availability, and a concomitant delay to theatre. Wu *et al.*[32] used a highly sensitive CRP in place of routinely available CRP demonstrating an improved sensitivity and specificity for identifying NSTI when compared with the original LRINEC. However, this particular CRP assessment is not widely available. Borschitz *et al.*[35] used clinical symptoms to score patients for risk of NSTI and found that this modification improved the positive and reduced the negative predictive values of the score. In all three modifications of the LRINEC there was no indication that PWID patients were included.

Table 8

Calibration and discrimination for NSTI and survival models

	Calibration	R^2	Dxy	*C*-index	Brier score
NSTI	0.949	0.283	0.587	0.794	0.144
Critical care survival	0.525	0.034	0.301	0.600	
Hospital survival	0.943	0.444	0.503	0.751	

NSTI, necrotising soft tissue infection.

The SIARI score (Site other than the lower limb, Immunosuppression, Age less than 60 years, renal impairment (creatinine >141 μmol/l), and inflammatory markers (CRP ≥ 150 mg/l, total leucocyte count $>25\times10^9$/l), reported a better discriminative ability than the LRINEC scoring system in the original studies. The SIARI score places importance on the anatomical site of the infection. There were no PWID detailed in the SIARI cohort[34]. Use of the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ failure Assessment (SOFA) scoring systems for sepsis do not help distinguish between NSTI and non-NSTI, and rather help to identify future morbidity and mortality[31]. A recent combined systematic review and meta-analysis incorporating 23 studies ($n=5982$) assessing the diagnostic accuracy of the LRINEC score, physical examination and imaging, demonstrated poor sensitivity of these tests in determining NSTI[20].

To date, no such scoring system has been validated for use specifically in the PWID population, for which the diagnosis of NSTI can be more challenging than in the general population. Using a LRINEC score ≥ 6 to identify NSTI in this cohort of patients, with a sensitivity of 73% and positive predictive value of 31%, highlights its poor ability to predict NSTI in PWID, with a poor specificity of 62% for correctly excluding NSTI. Despite respective high AUCs of 0.980 and 0.976 for the original LRINEC development and validation cohorts, within our cohort the AUC for the LRINEC discriminating NSTI from non-NSTI was only 0.697. This prompted our development of a visual, self-explanatory nomogram based upon binomial logistic regression analysis. This was internally validated in accordance with the TRIPOD recommendations[26].

The discriminatory power of a nomogram has been shown to be one of the most accurate tools for predicting outcomes in comparison with other methods, such as tree analysis, artificial

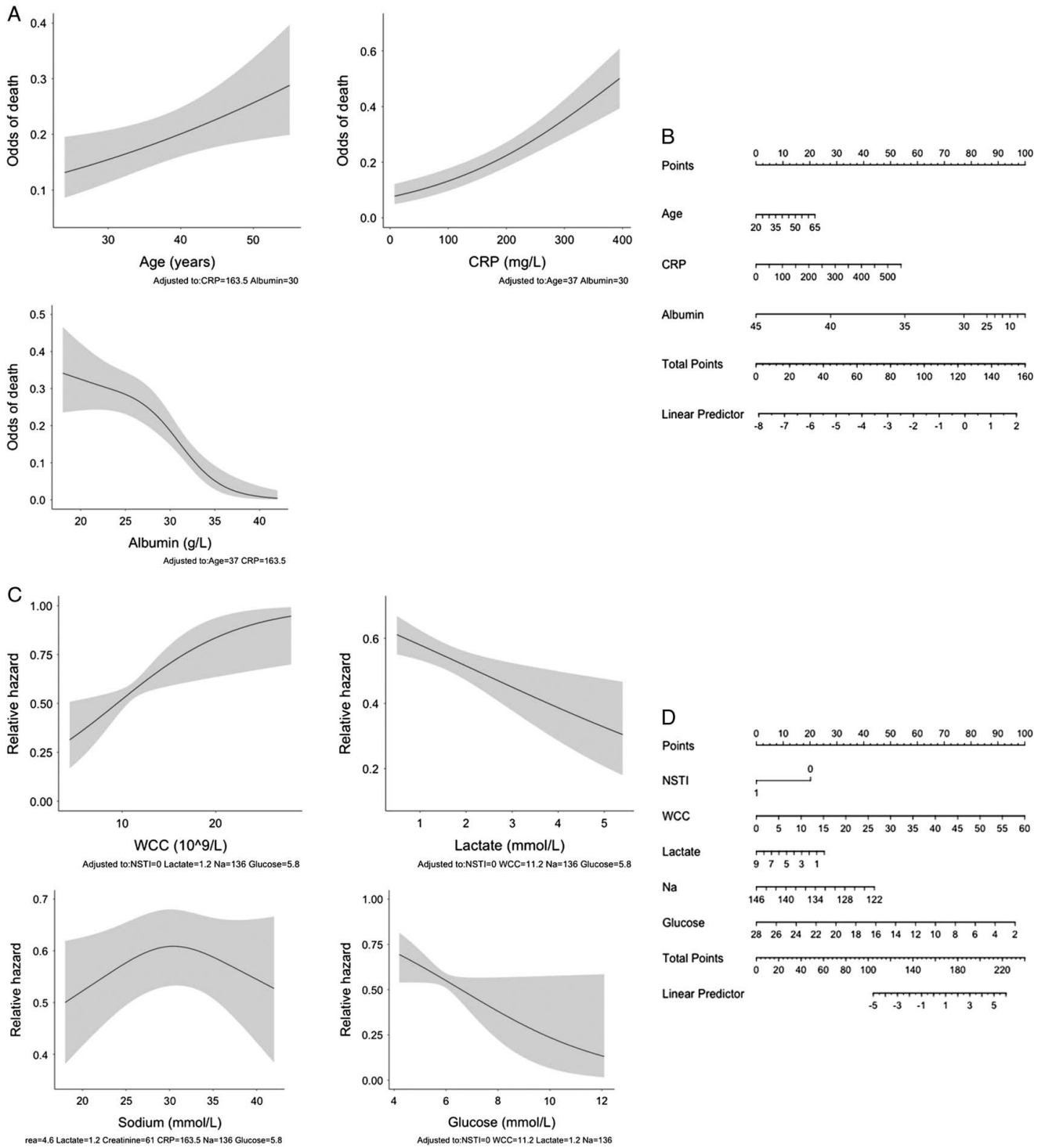


Figure 4. Outcome models. Nonlinearity attributed to continuous variables by attaching three cubic splines. Logistic model of necrotising soft tissue infections (NSTI) outcome (A) and corresponding nomogram: age, C-reactive protein (CRP) and nonlinear albumin were significant predictors of NSTI within our dataset (B). Best-fit Cox proportionality survival model for time to discharge from critical care (C) and corresponding nomogram: NSTI, white cell count (WCC), lactate, sodium and glucose provide best model (D). Best-fit Cox proportionality survival model for time to discharge from hospital (E) and corresponding nomogram: age, albumin, nonlinear creatinine, CRP, and glucose are significant predictors of hospital survival (F).

neural networks and risk grouping[36–39]. The nomogram is a widely accepted and reliable tool to create a simple to use, intuitive and interactive graph for predictive models that can quantify a clinical event[40].

Our nomograms were developed using the methodology recommended by Harrell[25]. We assumed non-linearity of continuous data and internally validated data using the bootstrap, employing the entire dataset for calibration and validation. The

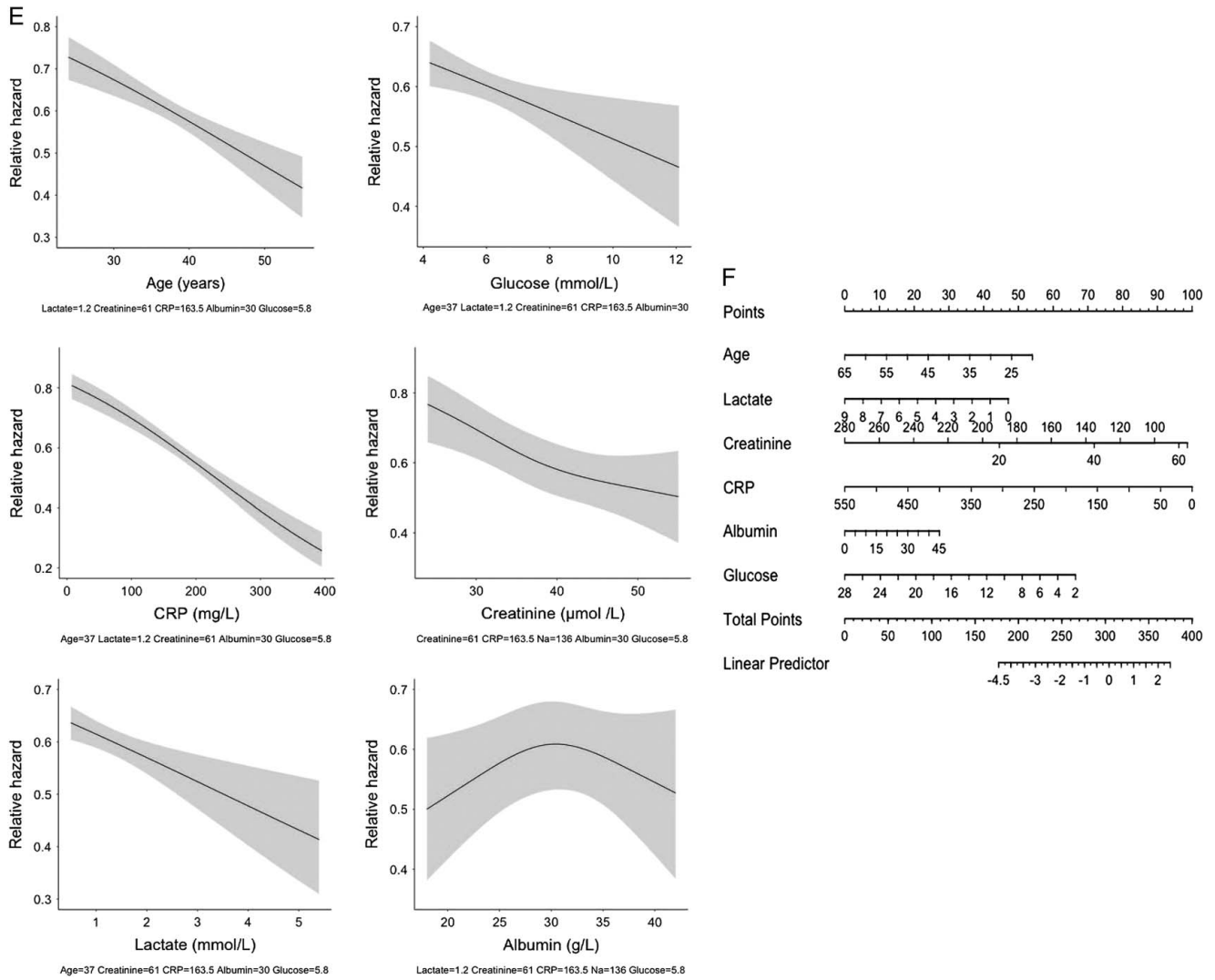


Figure 4. (Continued)

logistic regression model predicting the odds of developing NSTI in our patient cohort had a calibration of 0.949 and a *C*-index of 0.794, indicating reliable predictive ability for NSTI using age, CRP, and non-linear albumin in the developed nomogram. This contrasts with an AUC of 0.697 for the LRINEC score in our population for predicting NSTI.

The best-fit survival models (Cox proportional hazard regression analysis) for hospital survival and critical care survival, demonstrated only the hospital survival model was accurate. In both the logistic regression model for predicting NSTI and the Cox proportional regression model for hospital survival, CRP, and albumin were both strong predictors of outcome. With the limited resources available to community substance use teams, this survival nomogram could aid allocation of resources towards patients most at risk of death upon discharge from secondary care.

BBV testing was undertaken in only 19.7% of admissions, with detection of hepatitis C (not in treatment) in 25.5% of those tested. One case of hepatitis B and no unknown cases of HIV were identified. The low rate of BBV testing requires reflection, as this is a potential opportunity for harm reduction in this population, particularly given the 25.5% rate of hepatitis C diagnosis, which can generate discussion (sometimes re-discussion in those who have previously declined management) and commencement of treatment. These admissions, which can be recurrent, should be recognised as opportunities to reduce harm in PWID.

The retrospective nature of this study imposed several limitations that require further discussion. There was not complete haematological and biochemical parameter data available for the full dataset of 557 admissions, which restricted the number of admission episodes that the LRINEC could be applied to. This reflects a real-world scenario beyond the closely controlled confines of a trial assessing these markers for predictive purposes (not all patients with cellulitis may have warranted having their blood glucose checked, however it has highlighted variations in practice that should be considered). A total of 251 separate admission episodes could be compared, which exceeds the number used in the original LRINEC validation cohort ($n = 140$)[19]. Microbiology samples were also not sent for all patients.

We were unable to obtain data on the specific substances injected precipitating the admission. However, in Scotland (and the UK), especially in our region, heroin injecting predominates[8,41]. The types of drugs injected may influence the

inflammatory response and consequently the LRINEC score, although preparation practices involving the overuse of acidifiers, as is observed in the UK, may have a greater impact on inflammation causing chemical damage to vessels and perivascular soft tissues manifested in blood parameters[42,43]. This is an important consideration unique to PWID, possibly further contributing to diagnostic difficulty. It should be recognised that the causes of infection are multifactorial in this patient group. They include non-sterile injecting techniques, contaminated diluents (e.g. puddle or toilet cistern water or saliva), licking of needles, sharing injecting equipment, anatomical area of injecting, preceding contamination of the drugs in transit and higher risk injecting practices such as injecting subcutaneously or intramuscularly ('popping,' a practice particularly associated with the development of NSTI)[44–47]. This latter practice is increasingly observed in older injecting populations where intravenous or arterial access options become unavailable because of thrombosis or surgical intervention[43–47]. Some of these habits are reflected by the infecting organisms, such as needle licking and *Streptococcus anginosus*, the third most common bacteria implicated in NSTI in this study[46].

A further limitation when reporting on NSTI is the variability in diagnostic definition, with an element of experience required. As 93.5% of patients in this study were managed by the same vascular surgery department, this made diagnosis more consistent. The focus of this work was early diagnosis of NSTI in PWID, with the blood parameters recorded based upon initial admission. It is acknowledged though that the clinical picture is dynamic beyond initial admission blood parameters, and a relatively high index of suspicion for NSTI should remain as the situation evolves.

This study focused on the lower limb complications of injecting drug use as this represented the majority of admissions to our secondary care services. This is consistent with the high rate of groin injecting in our region, and in Scotland as a whole[14,41]. Further, over the past two decades groin injecting has been rising across the UK[8,48]. The lower limb complications of injecting drug use can also be more diagnostically challenging, compounded by chronically scarred, swollen and inflamed tissues at greater depth with probable features of venous insufficiency.

Finally, the nomogram generated in this study has not undergone external validation. In accordance with TRIPOD guidance, an additional study would be required to externally validate the nomogram. This would need to reflect a similar but separate population within a similar, yet separate geographical region conducted by a different team of researchers[26].

Conclusions

NSTI secondary to injecting drug use pose a challenge to clinicians across surgical and medical disciplines. Diagnosis is often delayed and the use of the LRINEC in this specific population was not shown to be beneficial in distinguishing NSTI from non-NSTI. The developed nomogram allows for a simple, intuitive graphical interface to supply clinicians with a likelihood for the presence of NSTI. This would provide the clinician with an early warning system, allowing for more expedient imaging, timely referral to an appropriate surgical specialty and subsequent urgent theatre. Ongoing clinician education surrounding NSTI, the necessity for a high index of suspicion, especially within the PWID population, and rapid cross-sectional imaging to allow for prompt and adequate surgical debridement remain key to reducing morbidity and mortality.

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Author contribution

All authors have made substantial contributions in terms of one or more of: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be submitted. All authors have read and complied with the author guidance.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

Research registration unqiue identifying number (UIN): researchregistry8204.

Guarantor

Caitlin S MacLeod, Hannah L O'Neill and Stuart A Suttie.

Data statement

Due to the sensitive nature of the subject of this work and also the clinical data used, our healthboard Caldicott Guardian stipulates that raw data should remain confidential and not be shared.

Provenance and peer review

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