Burns & Trauma, 2026, 14, tkag028
https://doi.org/10.1093/burnst/tkag028
Published: 14 April 2026
Review

OXFORD

Diagnostic strategies in necrotizing soft tissue infections: from clinical scores to multi-omics and machine learning

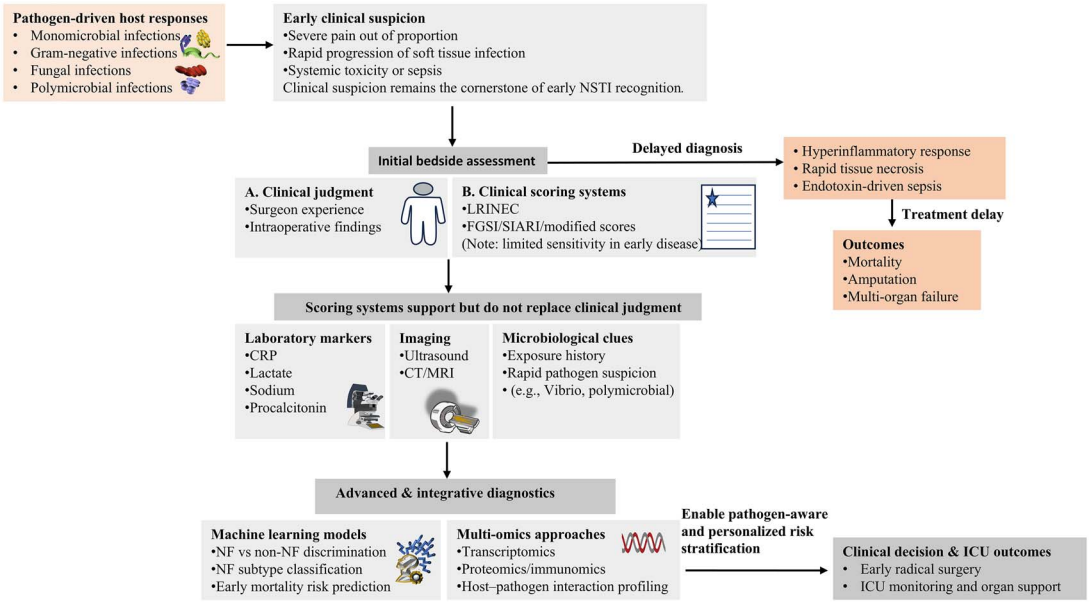
Xiaolin Ji[1,2], **Xinze Li**[1,2], **Zhongqiu Lu**[1,2,*]

[1]Department of Emergency, The First Affiliated Hospital of Wenzhou Medical University, Nanbaixiang Street, Ouhai District, Wenzhou, Zhejiang 325035, China
[2]Wenzhou Key Laboratory of Emergency and Disaster Medicine, Nanbaixiang Street, Ouhai District, Wenzhou, Zhejiang 325035, China
*Corresponding author. E-mail: lzhq@wmu.edu.cn

Abstract

Necrotizing soft tissue infections (NSTIs) represent a group of rapidly progressing, life-threatening infections characterized by widespread tissue necrosis, systemic inflammation, and multiorgan failure. Early diagnosis remains a clinical challenge because of nonspecific initial manifestations and overlapping symptoms with other soft tissue infections. Diagnostic scoring systems such as the Laboratory Risk Indicator for Necrotizing Fasciitis score and its variants have been widely utilized to facilitate early recognition but are limited by variable sensitivity and insufficient predictive value across diverse clinical populations. Recent advances in multi-omics technologies and machine learning approaches have enabled the identification of molecular biomarkers and predictive patterns associated with NSTI onset and progression. Integration of high-dimensional omics data with clinical and imaging parameters holds potential for dynamic, real-time diagnostic support, and individualized risk stratification in the intensive care setting. This review summarizes the evolution of diagnostic strategies for NSTIs, critically appraises the limitations of conventional clinical scoring systems, and examines emerging omics-based and ML-driven approaches. Finally, we propose an integrated diagnostic roadmap that aligns clinical assessment, imaging, microbiologic evaluation, host-response biomarkers, and multi-omics data to guide future research and clinical translation.

Graphical Abstract



Keywords Necrotizing soft tissue infections, Necrotizing fasciitis, Diagnostic scoring systems, Multi-omics biomarkers, Machine learning

Received: 9 October 2025. **Revised:** 2 April 2026. **Accepted:** 2 April 2026
© The Author(s) 2026. Published by Oxford University Press.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

Highlights

- **Early diagnosis of necrotizing soft tissue infections (NSTIs) remains challenging because the initial clinical features overlap with those of cellulitis and other clinical mimics.**
- **The Laboratory Risk Indicator for Necrotizing Fasciitis and related laboratory-based scores show variable sensitivities across settings and should not delay surgical consultation when NSTIs are clinically suspected.**
- **Imaging (computed tomography/magnetic resonance imaging/point-of-care ultrasound) can support triage, but no single modality is definitive, especially for hemodynamically unstable intensive care unit (ICU) patients.**
- **Multi-omics profiling (transcriptomics, proteomics, immunomics, and metabolomics) reveals pathogen- and host-response signatures that may improve diagnostic and prognostic stratification.**
- **Machine learning models integrating clinical, imaging, and omics data provide a framework for personalized risk prediction and an ICU-oriented diagnostic roadmap.**

Background

Necrotizing soft tissue infections (NSTIs) are fulminant, rapidly progressive infections that often culminate in septic shock and multiorgan failure requiring intensive care management [1–3]. They encompass a spectrum of clinical entities, including necrotizing fasciitis (NF), necrotizing cellulitis, and necrotizing myositis. Among these, NF is the most aggressive phenotype, with extensive tissue injury and widespread necrosis leading to persistently high mortality [2, 4–9]. Reported in-hospital mortality rates for NF vary widely, ranging from 10% to 75%, and are influenced by factors such as delayed surgical intervention, advanced age, hypotension, acidosis, bacteremia, renal dysfunction, hyponatremia, peripheral vascular disease, and the presence of myonecrosis or myositis [10].

Clinically, NSTIs are characterized by severe inflammation, progressive necrosis, and toxin-mediated injury. Without timely treatment, these features can rapidly progress to sepsis, multiorgan dysfunction, and death [11, 12]. Early manifestations—including erythema, swelling, and pain—are frequently nonspecific and often mimic benign conditions such as cellulitis or abscesses, thereby complicating timely recognition [13]. Despite advances in clinical and critical care, a substantial diagnostic gap remains. Only 15%–34% of NF patients receive an accurate diagnosis at the time of admission [1, 14], and overall mortality for NSTIs continues to range between 20% and 40%, largely because of delayed recognition and the fulminant progression of the disease [15–20].

To improve early identification, the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was developed as a diagnostic screening tool [21, 22]. However, subsequent validation studies have shown that its accuracy was initially overestimated. Reported sensitivities for a threshold of $\geq$6 range from 43.2% to 80.0%, and for $\geq$8, they range from 28.6% to 68.4% across different populations and clinical settings. Several studies have also highlighted its limited specificity [23, 24]. For example, Bennett (2008) reported a positive predictive value (PPV) for mortality of only 21% at the recommended threshold ($\geq$6), with substantial mortality still observed in patients below this cut-off, suggesting that the LRINEC reflects generalized inflammation rather than pathophysiological changes specific to NSTIs [25]. The score performs particularly poorly in high-risk populations, such as patients with diabetes, immunosuppression, or intravenous drug use, and its utility in patients with hematological malignancies is especially limited [6, 26–30]. Collectively, these data raise concerns about the incremental value of the LRINEC beyond careful clinical assessment in critically ill populations [23, 31–33]. Imaging modalities [computed tomography (CT), magnetic resonance imaging (MRI), and point-of-care ultrasound (POCUS)] can assist in decision-making, but none are definitive, and each may be constrained by clinical instability or resource availability in the intensive care unit (ICU).

Because NSTIs may evolve within hours, immediate surgical exploration and debridement—together with broad-spectrum antibiotics and aggressive sepsis management—remain the cornerstone of care, and each 24-hour delay is associated with a significant increase in mortality [2, 3, 9, 34, 35]. Accordingly, there is a pressing need for diagnostic strategies that accelerate triage and improve specificity without sacrificing sensitivity at the bedside [2, 35].

Recent advances in molecular diagnostics, particularly multi-omics technologies, have substantially improved the diagnostic and prognostic assessment of NSTIs [36, 37]. Integrative approaches combining transcriptomics, immunomics, and metabolomics have identified pathogen-specific and host-response biomarkers, providing valuable insights into NSTI pathophysiology [31, 36, 38]. Moreover, ML techniques are being increasingly applied to multi-omics datasets to enhance early detection, refine risk prediction, and support personalized treatment [39, 40]. The application of artificial intelligence (AI) to multi-omics data holds promise for closing current diagnostic gaps in NSTIs, particularly in the ICU, where early recognition is crucial. This review outlines the transition from conventional scores to AI and omics-based tools and considers their future integration into critical care workflows.

In this narrative review, we summarize the evolution and performance of existing diagnostic tools, critically appraise their applicability to critically ill patients, and outline an ICU-oriented framework that integrates clinical assessment, imaging, and multi-omics/ML approaches to close the diagnostic gap in NSTIs (Figure 1).

Review

Microbiological classification and pathogen-specific epidemiology of necrotizing soft tissue infections

The diverse microbiological spectrum and pathogen-specific epidemiology of NSTIs present significant challenges for clinical diagnosis and management. NSTIs constitute a heterogeneous group

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

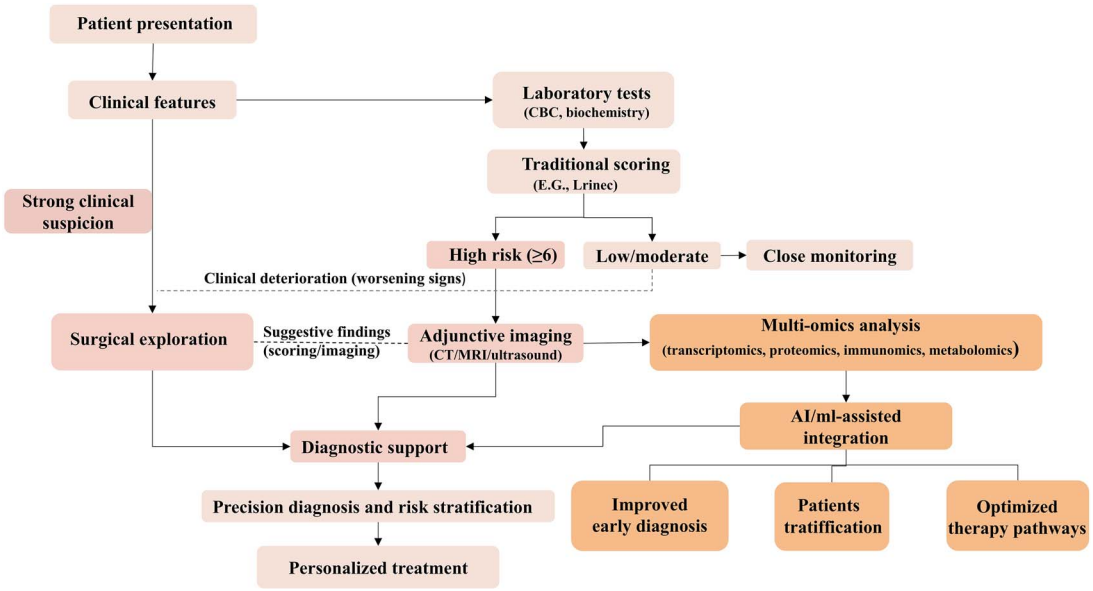


Figure 1 Conceptual flowchart of clinical diagnosis and risk stratification of necrotizing soft tissue infections. The pathway begins with patient presentation, clinical evaluation, laboratory testing, and Laboratory Risk Indicator for Necrotizing Fasciitis scoring, followed by surgical exploration in high-risk or strongly suspected cases. Adjunctive imaging and close monitoring assist in diagnosis, whereas multi-omics analysis integrated with artificial intelligence/machine learning models enhances precision diagnosis, risk stratification, and personalized treatment

of rapidly progressive infections with varying microbial etiologies, degrees of anatomical involvement, and clinical severity. NSTIs are traditionally classified into four types, polymicrobial (Type I), monomicrobial (Type II), and less common Types III and IV, which are associated with marine bacteria and fungi, respectively (Table 1) [10, 41]. Among these, Type I (polymicrobial) and Type II (monomicrobial) are the most prevalent. Type I infections are typically caused by a mix of aerobic and anaerobic organisms, whereas Type II infections are most often due to a single pathogen, commonly *Streptococcus pyogenes* [11, 42, 43]. Accurate and timely identification of the microbial etiology is crucial for guiding targeted antibiotic therapy and improving patient outcomes [9, 26]. However, overlapping clinical features among NSTI subtypes, difficulties in early pathogen detection, and the potential for rapid disease progression create substantial diagnostic challenges. Thus, prompt recognition of NSTI subtypes remains essential to minimize the morbidity and mortality associated with diagnostic delays.

Type I NSTIs represent the predominant subtype and are observed in 70%–80% of clinical cases [44–47]. They usually arise from polymicrobial infections involving both aerobic and anaerobic organisms and commonly originate in the gastrointestinal or genitourinary tract [48]. Patients with diabetes mellitus, peripheral vascular disease, or immunosuppression—especially those who have undergone recent surgical procedures—are at increased risk of developing this form of NSTI [48, 49]. Type II NSTIs are characterized by monomicrobial infections and are usually caused by gram-positive organisms, most commonly Group A Streptococcus (GAS) or *Staphylococcus aureus*, in ∼20%–30% of cases (including methicillin-resistant *S. aureus* [MRSA]) [43–46, 50, 51]. Given the prominent role of GAS in Type II NSTIs, recent epidemiological surveillance has attracted considerable attention. Notably, a recent analysis revealed that invasive GAS infections significantly increased across 10 U.S. states between 2013 and 2022, with the incidence increasing from 3.6 to 8.2 per 100 000 persons [52]. This form can affect individuals across all age groups, particularly previously healthy patients, particularly after trauma or surgical interventions, and may occur even in the absence of immunosuppression. Type III NSTIs are caused primarily by gram-negative monomicrobial pathogens, most notably marine-related Vibrio species such as *Vibrio vulnificus* [53] and *Vibrio damsela* [15, 42, 54–56]. These infections are predominantly reported in warm coastal regions and are strongly associated with seawater exposure or the ingestion of contaminated seafood [55, 57–60]. Although less common, Clostridium species have also been implicated in Type III infections [61]. Despite timely diagnosis and aggressive treatment, Type III NSTIs have a high mortality rate of 30%–40% [53, 60, 62]. Infections caused by marine Vibrio species are being increasingly recognized worldwide, with *V. vulnificus* NSTIs—manifesting as septicemia or necrotizing wound infections—being especially lethal, with case fatality rates exceeding 50% [63]. Kuehl *et al.* (2019) further proposed classifying all monomicrobial gram-negative NF as Type III, citing its higher mortality compared with that of Types I and II infections, particularly when due to Enterobacterales [42, 64]. These infections typically affect older patients with comorbidities such as liver cirrhosis or chronic kidney disease and are associated with poor outcomes [64, 65]. Type IV NF is attributed to fungal pathogens, which typically occur after traumatic injuries or burns, with Aspergillus and zygomycetes being the most frequently isolated organisms [45, 66, 67]. Candida-associated NF is exceedingly rare and is usually observed in immunocompromised patients [67].

Microbiological confirmation and diagnostic limitations of necrotizing soft tissue infections

Microbiological confirmation plays a central yet inherently limited role in the diagnosis of NSTIs [68]. The diagnosis of nonpurulent cellulitis is inherently difficult because of nonspecific clinical

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

Table 1 Classification and characteristics of necrotizing soft tissue infections

Type	Etiology	High-risk populations/triggers	Clinical features
Type I (Polymicrobial infections)	Mixed aerobes and anaerobes (e.g. *Escherichia coli*, Bacteroides, Enterococcus)	Diabetes, peripheral vascular disease, perianal or GI surgery	Most common; synergistic bacterial destruction
Type II (Monomicrobial infections)	GAS, *Staphylococcus aureus* (incl. MRSA)	Trauma, surgical wounds; may also affect healthy individuals; protean presentation easily missed; may progress to myonecrosis	Rapid progression; often associated with toxic shock
Type III (Gram-negative monomicrobial infections)	*Vibrio vulnificus*, *V. damsela*, Aeromonas spp.; occasionally Clostridium spp.	Seawater exposure, seafood ingestion, chronic ulcers; more frequent in warm coastal regions	Coastal prevalence; high mortality; fulminant course
Type IV (Fungal infections)	Opportunistic fungi (e.g. Candida, zygomycetes)	Immunosuppression; postoperative wounds; burns or trauma	Rare but lethal; diagnosis frequently delayed

Necrotizing soft tissue infections are classified into four types on the basis of their microbiological etiology: Type I, Type II, Type III, and Type IV. Each type differs in terms of risk factors, clinical setting, and disease severity. Data are summarized from previously published studies as cited in references [10, 11, 41–54]

features and the lack of a validated gold-standard test, which in turn complicates early differentiation from NSTIs [69]. Confirmatory cultures and histopathology therefore play a complementary role in excluding sterile necrotizing mimickers, despite limitations related to delayed availability, low yield, and skin contamination [70–72]. Interpretation is especially challenging when common colonizers such as *S. aureus* are isolated and require the integration of sampling depth, histopathology, organism burden, and specimen concordance rather than a reliance on culture results alone, underscoring the need for standardized diagnostic reference criteria [73].

Beyond microbiologic ambiguity, NSTI diagnosis is further complicated by early clinical overlap with sterile inflammatory dermatoses such as pyoderma gangrenosum (PG), Sweet's syndrome, and complex purpuric disorders, all of which may closely mimic necrotizing infection in terms of both inflammatory severity and skin necrosis-like appearance [74]. PG is a type of neutrophilic dermatosis characterized by severe pain and rapidly progressive ulceration with undermined borders and can closely resemble early NSTIs in terms of clinical presentation [75–77]. Sweet's syndrome may present with acute inflammatory skin lesions and systemic inflammatory features but is distinguished by the absence of deep tissue necrosis or invasive infection and by its characteristic response to immunosuppressive therapy [78]. Cutaneous vasculitic disorders may also manifest with purpura, bullae, or ulceration suggestive of NSTIs; however, these findings reflect primary vascular inflammation or occlusion, and skin biopsy remains critical for establishing the diagnosis [79]. Importantly, reliance on microbiologic results or isolated clinical findings alone is insufficient and may lead to inappropriate surgical intervention or delayed immunomodulatory treatment [69, 80, 81].

Limitations of traditional scoring systems

Inherent limitations of the Laboratory Risk Indicator for Necrotizing Fasciitis score

The nonspecific early presentation of NSTIs, frequently mimicking cellulitis or abscess, contributes to diagnostic delay and high mortality, prompting the development of scoring systems to assist in distinguishing necrotizing from non-NSTIs [42]. The LRINEC score, proposed by Wong *et al.* in 2004, integrates six laboratory parameters [C-reactive protein (CRP), white blood cell (WBC) count, hemoglobin (Hb), sodium (Na), creatinine, and glucose] into a composite index, with a cut-off of $\geq$6 points (Table 2) [21]. In the original cohorts, it demonstrated high sensitivity (89.9% and 92.9%) and high predictive performance [PPV 92.0%, negative predictive value (NPV) 96.0%]. These findings position the LRINEC as a potentially valuable tool for differentiating necrotizing from non-necrotizing infections in the emergency setting. However, its reliance solely on nonspecific laboratory data—without accounting for clinical presentation or imaging findings—raised concerns about its applicability in diverse patient populations and atypical cases [19]. Subsequent studies revealed substantial variability in LRINEC performance across populations and clinical settings (Table 3). While moderate accuracy was reported in some cohorts, multiple studies from Europe, Southeast Asia, and the United States reported substantially reduced sensitivity and frequent misclassification of high-risk NSTI patients, with limited improvement even at high cut-off values [82–85]. These discrepancies suggest that demographic, geographic, and pathogen-related factors significantly influence LRINEC performance, although relatively better accuracy has been reported in select populations [86]. These inconsistencies highlight a fundamental limitation of the LRINEC score: it relies exclusively on nonspecific laboratory values and does not incorporate clinical presentation, imaging features, or immune response dynamics. As a result, the LRINEC score often fails to capture early pathophysiological changes unique to NSTIs, reducing its sensitivity in high-risk subgroups and pathogen-specific settings. For example, in Vibrio-associated NF, only 11% of patients exceeded the LRINEC threshold despite high mortality [87]. Similarly, Hansen *et al.* (2017) reported no correlation between the LRINEC score and key inflammatory cytokines [interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)], underscoring its inability to reflect host immune activation [31]. Importantly, multiple studies have demonstrated that the LRINEC has limited prognostic value and was not designed to serve as a mortality prediction tool. Large cohort and contemporary studies have repeatedly demonstrated poor discriminatory ability for mortality, despite the identification of other independent prognostic factors, such as age, comorbid

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

Table 2 Laboratory risk indicators for the Laboratory Risk Indicator for Necrotizing Fasciitis scoring system

Parameter	Thresholds	Points
CRP	<15 mg/dL	0
	≥ 15 mg/dL	4
WBC count (/mm^3)	<15	0
	15–25	1
	≥ 25	2
Hemoglobin (g/dL)	>13.5	0
	11–13.5	1
	<11	2
Sodium (mmol/L)	≥ 135	0
	<135	2
Creatinine (mg/dL)	<1.6	0
	≥ 1.6	2
Glucose (mg/dL)	<180	0
	≥ 180	1

Maximum score = 13 points; score <6: NF cannot be excluded; score ≥ 6: suggests high risk, NF should be considered; and score ≥ 8: strongly associated with necrotizing soft tissue infection and high risk. Data are summarized from previously published studies, as cited in references [19, 21, 42]

cardiovascular disease, lactic acidosis, bacteremia, radiographic gas, and multiorgan dysfunction [29, 88–90].

Clinical consequences of diagnostic delays

Delayed diagnosis and surgical intervention are the principal determinants of mortality in NSTIs [91, 92], with reported amputation rates ranging from 21% to 60% [16, 93, 94]. Surgical delay beyond 12 hours is consistently associated with increased mortality, underscoring the critical importance of early and aggressive surgical management [42, 95, 96]. Cohort data demonstrate that initial nonsurgical management or interhospital transfer usually prolongs the time to surgical intervention, while case-based evidence shows that low or falsely reassuring LRINEC scores may delay exploration despite the development of necrotizing infection [97–99]. Collectively, these findings reinforce that clinical judgement and early surgical consultation must take precedence over scoring systems when NSTI is suspected [97–99].

Taken together, these findings underscore that the LRINEC should remain an adjunctive screening tool and must not delay surgical consultation or exploration when NSTI is clinically suspected.

Modified scoring systems and imaging for diagnosis

Borschitz *et al.* (2015) refined the LRINEC by adding clinical features, particularly ‘pain out of proportion’, and incorporating discriminative markers such as elevated CRP levels, thereby improving its PPV without compromising specificity [13]. Wu *et al.* (2021) further refined the LRINEC by adding diabetes, kidney disease, and high-sensitivity CRP, resulting in a modified version, the modified LRINEC (m-LRINEC), demonstrating improved discrimination compared with the original LRINEC score [94]. A similar modification, the MLRINEC, developed by Wu P. H. *et al.* (2021), incorporated serum lactate levels and liver disease, improving sensitivity (91.8%) and specificity (88.4%) by accounting for comorbidities and dynamic clinical parameters [100]. An overview of the modified LRINEC and alternative scoring systems is presented in Table 4.

Several alternative scoring systems have been developed to overcome the limitations of the LRINEC, including the Site of Infection, Immunosuppression, Age, Renal function, and Inflammatory markers score (SIARI) and the Laboratory Risk Indicator for Necrotizing Fasciitis score (LARINF), which integrate clinical context and inflammatory markers and demonstrate improved diagnostic or prognostic performance in selected populations [102,104]. For Fournier’s gangrene (FG), Fournier’s Gangrene Mortality Index (FGMI) includes age, creatinine level, albumin level, lymphocyte percentage, and the neutrophil-to-lymphocyte ratio (NLR), achieving an area under the curve (AUC) of 0.88 and outperforming the LRINEC in predicting mortality risk [105]. In addition to modified LRINEC-based models, mortality-focused tools such as the Necrotizing Soft Tissue Infection Mortality Score (NECROSIS) incorporate early clinical signs and laboratory abnormalities to support risk stratification, although further validation is needed [106]. Consistent findings from subsequent studies indicate that hyponatremia, elevated WBC count, low hematocrit, advanced age, anemia, and multiple wound sites are stronger predictors of mortality and amputation risk in NSTIs than the LRINEC score is [109,110]. Although advanced tools such as the Japanese Laboratory Risk Indicator for Necrotizing Fasciitis (J-LRINEC) have demonstrated improved diagnostic performance, their clinical adoption remains limited because of complexity, while additional indices, including the Systemic Immune–Inflammation Index (SII), Charlson Comorbidity Index (CCI), and elevated international normalized ratio (INR >1.5), have been identified as independent predictors of mortality in patients with NF and sepsis [107,111,112]. Importantly, pathogen-specific studies further highlight the prognostic heterogeneity of NSTIs, which cannot be adequately captured by laboratory-only scoring systems. In patients with Aeromonas- and Vibrio-associated NF, mortality has been linked to bloodstream infection, shock, skin necrosis, ineffective antimicrobial therapy, seawater exposure, hyperlactatemia, and low fibrinogen levels, underscoring the influence of microbial etiology and the host response on disease severity and outcome [113,114]. Imaging plays a crucial role in diagnosing NSTIs, especially when laboratory scores fail to provide definitive differentiation. Studies have demonstrated that fascial involvement, a lack of fascial enhancement, and fluid along the deep fascia on CT are strongly associated with NF, outperforming the LRINEC score in early diagnosis [115–117]. The MRINEC algorithm, which incorporates MRI findings such as T2 hyperintensity of the deep fascia, has achieved 94% sensitivity in distinguishing NF from cellulitis, even among patients with low LRINEC scores [103]. POCUS enables rapid bedside assessment of fascial thickening and fluid collection with high sensitivity [118], whereas near-infrared spectroscopy (NIRS) can be used to differentiate cellulitis from NF on the basis of significantly lower oxygen saturation in NF patients [119]. Collectively, these findings suggest that while modified scoring systems and imaging can support clinical assessment, timely surgical evaluation cannot be replaced when NSTI is suspected.

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

Table 3 Validation of the Laboratory Risk Indicator for Necrotizing Fasciitis score in different populations and clinical settings

Population	Cut-off	Sensitivity	Specificity	Key findings/notes	Study/year
Singapore, 2 hospitals (89 NF/225 controls; validation n = 140)	≥6	Dev: 89.9% Val: 92.9%	Dev: 96.9% Val: 91.6%	Original derivation/validation; excellent accuracy in initial cohorts	Wong et al., 2004 [21]
Australia, tertiary center (28 suspected NF, 10 proven)	≥6	80.0%	67.0%	Moderate accuracy; highlighted limitations in general use	Holland et al., 2009 [82]
Taiwan, Vibrio NF	—	11% met cut-off	—	Poor capture of pathogen-specific features; high mortality	Tsai et al., 2010 [87]
Northern Europe (74 NF)	≥6	43.2%	—	Markedly low sensitivity; limited applicability	Al-Hindawi et al., 2017 [83]
NF patients, immunological assessment	—	—	—	No correlation with cytokines (IL-6, TNF-α); lacks immune profiling	Hansen et al., 2017 [31]
Malaysia (44 suspected/confirmed NF)	≥6 ≥8	59.3% 48.1%	47.1% 58.8%	Low sensitivity and specificity	Syed et al., 2017 [84]
Australia, Northern Territory (98 NF/205 controls)	≥5	76.3%	93.1%	Relatively high accuracy; authors emphasized role of clinical suspicion	Narasimhan et al., 2018 [86]
Spain, Hematology patients (29 NF; gram-negative predominant)	≥6	—	—	Early mortality higher in gram-negative NF; LRINEC failed to predict outcomes	Albasanz-Puig et al., 2020 [29]
U.S. cohort (115 NF)	—	—	—	Mortality linked to age, CAD, CKD, lactic acidosis, MODS; LRINEC AUC = 0.56 (poor prediction)	Karnuta et al., 2020 [88]
Germany, Nuremberg (125 NF/319 STI)	≥6	59.0%	82.0%	Limited sensitivity; unsuitable for reliable diagnosis/prognosis	Breidung et al., 2023 [89]

Multiple validation studies have demonstrated wide variability in the sensitivity and specificity of the Laboratory Risk Indicator for Necrotizing Fasciitis score. While the initial cohorts reported good performance, subsequent studies showed reduced accuracy across geographic regions and patient subgroups, highlighting its limited generalizability. *STI* surgically treated soft tissue infection, *CAD* coronary artery disease, *CKD* chronic kidney disease *MODS* multiple organ dysfunction syndrome, *AUC* area under the receiver operating characteristic curve, *Dev* derivation, *Val* validation

Multi-omics biomarkers and molecular signatures in necrotizing soft tissue infections

Transcriptomics in necrotizing soft tissue infections diagnosis and prognosis

Recent transcriptomic studies have highlighted both pathogen- and host-specific signatures that hold diagnostic value in NSTIs. Imöhl *et al.* (2017) analysed *S. pyogenes* isolates in Germany and reported associations of specific emm types (e.g. emm1 and emm28) and superantigen genes (speA, speG, and speJ) with severe clinical phenotypes such as NF and sepsis [38]. In a murine NF model, Hirose *et al.* (2019) reported significant transcriptional reprogramming involving 483 genes, including virulence determinants such as sagA (streptolysin S precursor), speB (cysteine protease), and spd (secreted DNase), reflecting pathogen adaptation to the inflammatory microenvironment [120]. Similarly, Jahagirdar *et al.* (2022) demonstrated that monomicrobial GAS infections were enriched in host cytokine-related genes (e.g. IL1R2 and IL18R1), whereas polymicrobial infections upregulated the expression of chemokine-associated genes (e.g. STAT1 and CXCL9). These findings indicate that transcriptomic profiling can distinguish etiological subtypes of NSTIs and provide early stratification in clinical practice [40].

Further mechanistic insights underscore the role of transcriptomics in revealing host–pathogen interactions. The soluble M1 protein of *S. pyogenes*, particularly its B-repeat domain, was shown to activate the NOD-like receptor family pyrin domain–containing 3 (NLRP3) inflammasome through potassium efflux and clathrin-mediated uptake, driving caspase-1-dependent IL-1β release and pyroptotic cell death [121]. In murine models, extracellular M1 protein alone was sufficient to trigger IL-1β secretion, underscoring its dual function as an early immune signal and mediator of hyperinflammation in invasive infections such as NF and streptococcal toxic shock syndrome [121]. Complementary genomic and transcriptomic studies have further revealed mechanisms of persistence and virulence regulation, including fibrinolysis-driven immune evasion [122], fabT mutations, and rocA variable-number tandem repeat (VNTR) deletions [123,124], as well as unique genomic islands and phage elements in virulent *S. aureus* strains [125]. Beyond prognostication, transcriptomic and immunologic profiling may also aid early differentiation of true bacterial SSTIs from inflammatory mimics (pseudocellulitis), a clinically common source of misdiagnosis; however, evidence remains preliminary and is limited by the lack of a gold standard reference [71]. Collectively, these data highlight the diagnostic utility of transcriptomic profiling for identifying high-risk strains, stratifying infection subtypes, and guiding early therapeutic intervention.

Metabolomics in necrotizing soft tissue infection diagnosis and prognosis

Metabolomic profiling is a powerful tool for identifying biomarkers that capture both physiological and pathogenic processes in

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

Table 4 Modified LRINEC models and alternative scoring systems for diagnosing necrotizing soft tissue infections

Study (year)	Population	Model	Cut-off value	Sensitivity (%)	Specificity (%)	Key notes
Borschitz et al., 2015 [13]	29 NF and 59 cellulitis	LRINEC mod and clinical symp	≥6	93	80	Added 'pain out of proportion' + high CRP; improved prediction without loss of specificity
			≥8	83	90	
		LRINEC	≥6	83	89	
			≥8	48	93	
Huang et al., 2015 [101]	39 *Vibrio vulnificus* NSTI patients	MELD	≥20	80	97	MELD AUC = 0.929, useful for mortality monitoring
		ΔMELD	≥2	80	88	ΔMELD AUC = 0.897
Cribb et al., 2019 [102]	138 NF and 142 severe cellulitis	SIARI	≥3 (dev)	81	73	Outperformed LRINEC in both cohorts
			≥3 (val)	84	70	
		LRINEC	≥6 (dev)	59	63	Poorer discrimination than SIARI
			≥6 (val)	61	65	
Kim et al., 2020 [103]	61 NF and 28 severe cellulitis (49 MRI)	MRINEC	two-step decision tree	94	60	MRI findings: T2 hyperintensity of deep fascia; high sensitivity for NF detection
			≤5	88	69	
			6–7		0	
			97		-	
Wu et al., 2021 [94]	59 NF and 118 Non-NF	m-LRINEC	17	93.2	86.9	Added diabetes, kidney disease, hs-CRP (high-sensitivity CRP)
Wu et al., 2021 [100]	303 patients (101 NF *vs* 202 non-NF)	MLRINEC	≥12	91.8	88.4	Added serum lactate, liver disease; redefined cut-offs
Breidung et al., 2022 [104]	86 NF and 64 severe cellulitis	LARINF	≥5	84	75	Combines Hb, CRP, procalcitonin, comorbidities; superior to LRINEC and SIARI
Yönder et al., 2024 [105]	169 FG patients (20 deaths, 11.8%)	FGMI	≥5 (high risk)	90	70	Five parameters: age, Cr, Alb, lymphocyte %, NLR; outperformed LRINEC
Kim et al., 2024 [106]	362 suspected NSTIs, 297 confirmed NSTIs	NECROSIS	-	-	-	c-statistic 0.75; simple clinical index, validated across cohorts
Norimatsu et al., 2025 [107]	265 patients (56 NF, 209 cellulitis)	J-LRINEC	-	91.4	84.8	Regional variables, superior to LRINEC, complex to calculate
Bolat et al., 2025 [108]	Fournier's gangrene patients	glucose	≥186.5 mg/dL	83.8	83.3	Glucose >186.5 mg/dL associated with higher mortality, outperforming LRINEC
		NLR	≥14.04	83.3	76.7	

LRINEC Laboratory Risk Indicator for Necrotizing Fasciitis score, *m-LRINEC* modified LRINEC, *MLRINEC* modified LRINEC incorporating lactate and liver disease, *J-LRINEC* Japan-modified LRINEC, *MRINEC* magnetic resonance imaging-based LRINEC algorithm, *MELD/AMELD* Model for End-Stage Liver Disease/adjusted MELD, *SIARI* site, immunosuppression, age, renal function, inflammatory markers, *LARINF* lactate, albumin, renal function, inflammatory markers

NSTIs (Figure 2). Afzal *et al.* (2020) applied untargeted gas chromatography–mass spectrometry (GC–MS) profiling and network analysis to identify metabolites associated with NSTIs, including ornithine, ribose, urea, and glucuronic acid. These metabolites not only showed differential abundance but also modulated GAS growth and biofilm formation, highlighting their potential as both diagnostic biomarkers and mechanistic mediators of NSTI pathogenesis [36]. Additionally, metabolic biomarkers have been linked to disease severity in NSTI patients. Hansen *et al.* (2018) reported a reduced L-arginine/asymmetric dimethylarginine (ADMA) ratio as an independent predictor of mortality, demonstrating the prognostic significance of nitric oxide pathway dysregulation in NSTIs [37].

Subsequent studies have consistently reinforced the prognostic importance of renal and metabolic dysfunction in NSTIs. Elevated creatinine levels and a reduced estimated glomerular filtration rate (eGFR) have been identified as independent predictors of in-hospital mortality [126]. Building on this, Liu *et al.* (2022) developed a multivariable mortality risk model that incorporates renal function (creatinine), muscle injury (CK), coagulation parameters (PT), and invasive ventilation and achieved excellent discrimination (AUC 0.94) [127].

Immunomics and proteomics in necrotizing soft tissue infection prognosis

Immunomic profiling, particularly the measurement of acute-phase reactants, has gained attention as a powerful tool for diagnosing and prognosticating NSTIs. Procalcitonin (PCT) is a biomarker that has shown superior diagnostic performance compared with the LRINEC score. A study by Kishino *et al.* (2021) demonstrated that serum PCT, with a cut-off of 1.0 ng/ml, achieved 88% sensitivity, 89% specificity, and an NPV of 93%,

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

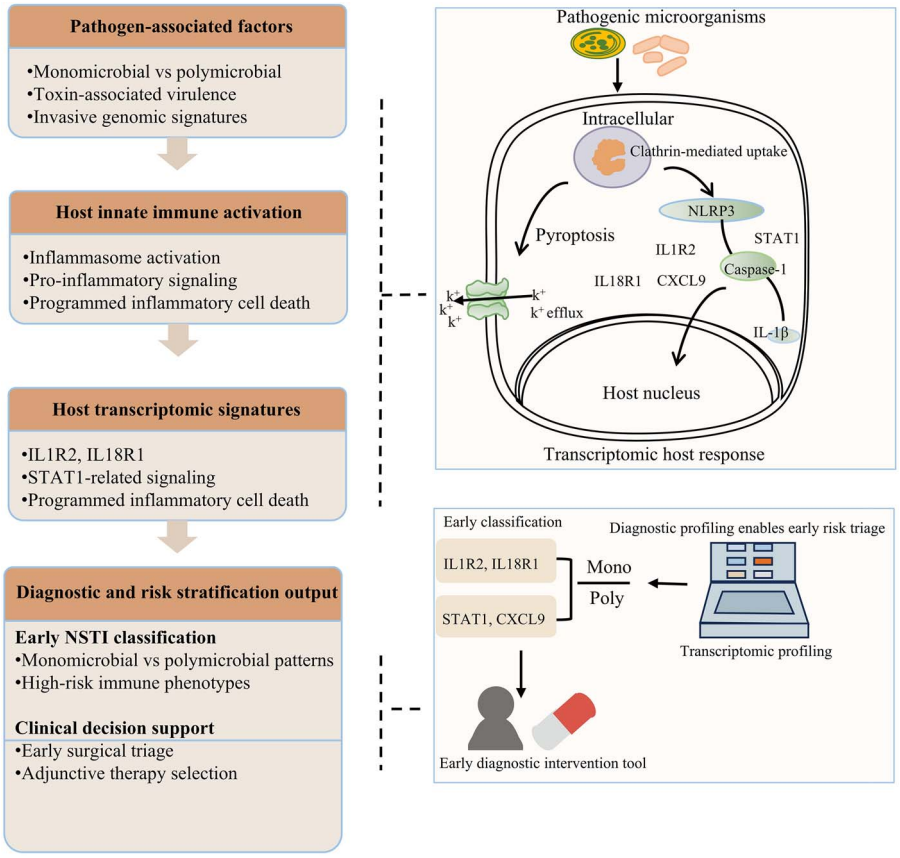


Figure 2 Genomic and transcriptomic biomarkers of NSTIs may support early diagnosis and risk stratification. Pathogenic microorganisms contribute to NSTIs via distinct genomic features. Bacterial components trigger host inflammasome activation, pyroptosis, and a transcriptional response involving IL1R2, IL18R1, CXCL9, and STAT1. Host transcriptomic profiling enables early immune classification and supports diagnostic triage in NSTI patients. *NSTIs* necrotizing soft tissue infections, *IL1R2* interleukin-1 receptor type 2, *IL18R1* interleukin-18 receptor type 1, *STAT1* signal transducer and activator of transcription 1, *CXCL9* C-X-C motif chemokine ligand 9, *NLRP3* NOD-like receptor family pyrin domain containing 3, *IL-1β* interleukin-1 beta

establishing PCT as a valuable rule-out biomarker for low-risk NF in the emergency setting [128]. In odontogenic NSTIs and FG, simple hematologic and inflammatory indices such as the SII, CRP + NLR, NLR, and CRP/prealbumin (PAB) ratio have shown strong diagnostic and prognostic accuracy and often outperform the LRINEC in early risk stratification [129, 130]. These findings underscore the role of biomarker profiling in early diagnosis and highlight the importance of host immune responses in NSTI progression. In a large-scale prospective study, Hansen *et al.* (2017) reported that patients with streptococcal NSTI exhibited significantly elevated levels of proinflammatory cytokines such as IL-6, IL-10, and TNF-α, with IL-6 being the most strongly correlated with disease severity [31]. This study demonstrated the utility of cytokine profiling for identifying systemic inflammation and assessing the severity of NSTIs, identifying IL-6 and TNF-α as key diagnostic and prognostic biomarkers [31]. Notably, high baseline pentraxin 3 (PTX3) levels are associated with increased mortality risk, further emphasizing the importance of immune and inflammatory biomarkers [131]. In addition to these immune markers, Chella Krishnan *et al.* (2016) reported that host genetic variations, including multiple quantitative trait loci, influence the outcomes of NSTIs, with IL-1β acting as a critical mediator [132]. Building on this, LaRock *et al.* (2020) demonstrated that GAS exploits SpeB-mediated IL-1β activation to facilitate neutrophil-driven bacterial colonization and infection, demonstrating pathogen-mediated manipulation of host inflammatory pathways [133]. These findings are consistent with those of Saijo *et al.* (2024), who reported that early GAS-NSTI patients often exhibited disproportionately elevated CRP levels despite normal WBC counts, suggesting that discordant biomarker patterns may represent early diagnostic indicators [134]. Understanding these genetic and immune mechanisms not only provides insight into the pathophysiology of NSTIs but also offers a promising avenue for developing more precise diagnostic tools and targeted therapies. In a large prospective multicenter cohort, Palma Medina *et al.* profiled 36 circulating immune and endothelial proteins and identified thrombomodulin as a highly accurate biomarker for NSTI detection (AUC = 0.95) [135]. Distinct cytokine and tissue-remodeling signatures (IL-2, IL-10, IL-22, CXCL10, Fas ligand, and MMP-9), together with shared shock-associated markers (G-CSF, S100A8, and IL-6), differentiated monomicrobial from polymicrobial NSTIs and were associated with septic shock risk, supporting proteomics-based phenotypic and prognostic stratification [135]. In patients with Group A streptococcal NSTIs, Bergsten *et al.* demonstrated a dose–response relationship between IVIG administration and plasma neutralization of streptococcal superantigens, indicating measurable functional immune modulation [136]. Such immune readouts are unlikely to support rapid bedside diagnosis but may enable diagnostic refinement through biological phenotyping, helping identify subgroups with

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

distinct host–pathogen interactions and differential therapeutic responsiveness.

However, coagulation abnormalities constitute a pivotal determinant of disease progression. Coagulopathy, in particular, has emerged as a significant marker of systemic organ failure and worsened prognosis. For instance, Ling *et al.* (2021) demonstrated that an elevated international normalized ratio (INR >1.5) was a strong independent predictor of mortality in patients with NSTIs, highlighting its role as a prognostic marker for severe disease [112]. Furthermore, Johnson *et al.* (2023) proposed an immunocoagulopathy-based model that incorporated platelet count, neutrophil count, and age and achieved an impressive AUC of 0.829 for in-hospital mortality prediction [137]. This model outperformed the LRINEC score and emphasized the value of the routine complete blood count as an accessible tool for risk stratification. Moreover, thrombocytopenia, another hallmark of coagulation dysfunction, has been identified as a powerful independent predictor of mortality [137]. Together, these findings highlight that both immune markers and coagulation abnormalities serve as critical components for understanding the pathophysiology of NSTIs and improving risk prediction, paving the way for more refined, multidimensional diagnostic models.

Translational applications and machine learning integration

The integration of multi-omics data, including transcriptomic, proteomic, and metabolomic profiles, into machine learning (ML)-based diagnostic platforms is a promising avenue for enhancing early diagnosis and risk prediction in NSTIs. The functional annotation of the core genes of *S. pyogenes*, such as scfA and scfB, has provided key molecular signatures that can be incorporated into multi-omics and AI diagnostic strategies targeting severe soft tissue infections [138]. Integrating multi-omics data with AI-driven analytics offers the potential to generate personalized diagnostic and prognostic models, thereby enhancing early detection, patient stratification, and treatment optimization in NSTIs.

Machine learning in necrotizing soft tissue infection diagnosis

ML is being increasingly applied to optimize the diagnosis and risk stratification of NSTIs. Jahagirdar *et al.* (2022) applied unsupervised clustering and random forest models to host–pathogen transcriptomic data to differentiate monomicrobial from polymicrobial NSTIs, thereby capturing etiologically and biologically distinct disease phenotypes rather than performing NSTI versus non-NSTI classification [40]. In the large INFECT cohort ($n = 409$), Katz *et al.* (2022) developed a random forest-based decision support system that identified 16 early sepsis-related variables (e.g. lactate, urine output, and blood pressure) to predict in-hospital mortality in NSTI patients, achieving an AUC of 0.91 and outperforming the Sequential Organ Failure Assessment (SOFA) score, even when limited to variables available within the first hour of admission, highlighting the potential of ML for accurate early mortality risk prediction in NSTIs [39]. An overview of ML applications in NSTI diagnosis and prognosis is summarized in Table 5. In addition to clinical prediction, ML has been integrated with omics data. HBOmic studies have used transcriptomic profiling and ML to evaluate responses to hyperbaric oxygen therapy, identifying molecular endotypes and biomarkers (e.g. NAT10, DNAJA3, and MTCO2P12) associated with immune restoration and therapeutic responsiveness [139, 140]. Importantly, this approach provides a framework for individualized adjunctive therapy in NSTI-associated sepsis. Similarly, Chang and Wu (2024) applied an interpretable Light Gradient Boosting Machine (LightGBM) model to distinguish NF from cellulitis and to further classify NF into *V. vulnificus* and non-Vibrio subtypes, achieving an AUC of 0.86, with SHapley Additive exPlanations (SHAP) analysis identifying key clinical and exposure-related predictors [141]. Collectively, these studies demonstrate that ML, particularly when integrated with clinical and multi-omics datasets, enhances diagnostic precision, facilitates early mortality risk prediction, and enables individualized risk stratification for patient management.

Challenges and limitations of multi-omics and machine learning in necrotizing soft tissue infection diagnosis

Despite the promising insights provided by multi-omics and ML studies in NSTIs, several methodological limitations must be acknowledged. Most available omics datasets are derived from small, single-center cohorts with substantial heterogeneity in patient characteristics, sampling time points, and analytical platforms, which limits their reproducibility and generalizability. In addition, many studies remain exploratory in nature and lack independent validation cohorts or prospective clinical integration, thereby constraining their immediate translational impact.

Importantly, the current generation of multi-omics platforms is constrained by turnaround time, technical complexity, and cost, which precludes their routine use in real-time bedside diagnosis or determination of surgical timing in acute NSTIs. While these approaches may improve biological understanding and retrospective diagnostic accuracy, it remains unrealistic to expect most omics-based assays to meaningfully accelerate first debridement decisions within current clinical workflows. This limitation represents a critical barrier that must be clearly recognized when interpreting their clinical potential. Rather than serving as immediate diagnostic tools, emerging evidence suggests that multi-omics approaches may be better positioned to support post-diagnostic risk stratification and treatment individualization after NSTI has been confirmed. Biomarker-guided immune and molecular profiling may help identify biologically distinct patient subgroups with differential responses to adjunctive therapies. For example, in Group A streptococcal NSTIs, Bergsten *et al.* demonstrated a dose–response relationship between intravenous immunoglobulin administration and plasma neutralization of streptococcal superantigens, supporting the concept that functional immune readouts could be leveraged to identify patients most likely to benefit from IVIG and to inform dosing strategies [136].

From an ML perspective, progress in NSTI research will likely require moving beyond isolated single-center models toward larger, multi-institutional efforts. Promising directions include multimodal models that combine clinical variables with microbiology and omics signals, as well as collaborative training strategies (e.g. federated learning) that allow models to be developed across sites while keeping patient-level data within local governance frameworks. Such approaches could help address data scarcity, improve robustness across settings, and support the development of clinically generalizable tools.

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

Table 5 ML applications for necrotizing soft tissue infections diagnosis and prognosis

Study (year)	Method	Key features/data	Performance	Clinical utility
Jahagirdar et al., 2022 [40]	Unsupervised clustering random forest	16S rRNA sequencing, host–pathogen gene expression	Reliable classification of monomicrobial versus polymicrobial infections	Molecular stratification of infection types
Katz et al., 2022 [39]	Random forest (Boruta selection)	16 sepsis-related clinical variables (e.g. lactate, urine output, SBP)	AUC 0.91 *vs* SOFA 0.77	Early mortality prediction; robust DSS
Vinkel et al., 2022 [139]	Unsupervised clustering ML integration	Whole-blood and tissue transcriptomics pre/post HBO_2	Identified treatment-responsive signatures	First omics–ML integration to assess HBO_2 therapy
Vinkel et al., 2025 [140]	ML transcriptomic profiling	Gene markers (NAT10, DNAJA3, MTCO2P12)	Stratification of HBO_2 responders	Biomarkers for precision therapy
Chang & Wu, 2024 [141]	LightGBM SHAP	Clinical + exposure predictors (lactate, CRP, hypotension, seafood exposure)	AUC 0.86, Sens 87.2%, Spec 74.5%	Differentiation of Vibrio NF using interpretable ML model

AUC area under the curve, *Sens* sensitivity, *Spec* specificity, *HBO_2* hyperbaric oxygen therapy

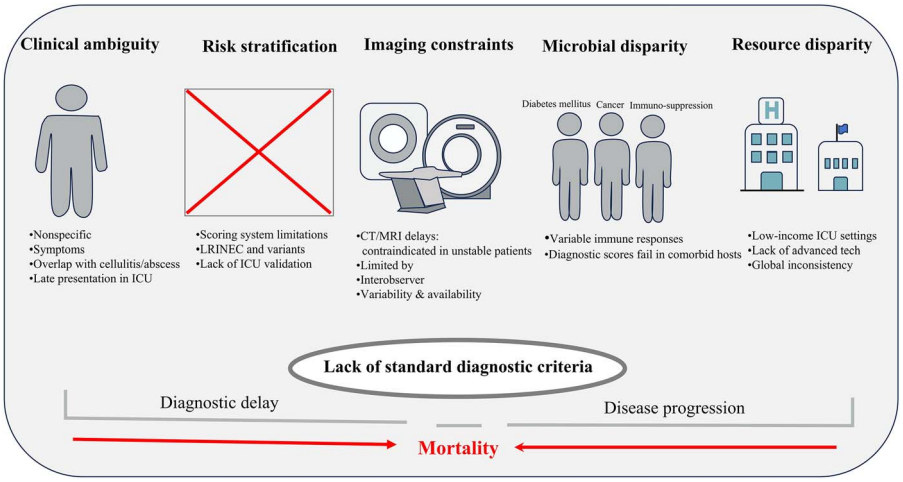


Figure 3 Multifactorial barriers to timely necrotizing soft tissue infections diagnosis in ICU settings. Diagnostic delays in NSTIs arise from overlapping clinical features, limited scoring tools, imaging constraints, microbial heterogeneity, and resource disparities, culminating in increased mortality

Challenges and future directions of necrotizing soft tissue infection diagnosis in critical care settings

NSTIs remain diagnostically challenging, especially in the ICU setting, as their early clinical manifestations are often nonspecific and overlap with those of benign soft tissue infections, leading to frequent misdiagnosis, delayed surgical intervention, and worse clinical outcomes [142, 143]. In parallel, recent multidisciplinary guideline efforts, such as the 2025 Consensus on the Diagnosis and Treatment of Adult Necrotizing Fasciitis, emphasize the lack of standardized diagnostic and treatment protocols and provide evidence-informed recommendations to support clinical standardization [144]. Traditional laboratory-based risk stratification tools, particularly the LRINEC score and its derivatives (e.g. m-LRINEC, MLRINEC, SIARI, and LARINF), demonstrate limited sensitivity, specificity, and external validation in heterogeneous ICU populations, with their performance further compromised by the confounding effects of critical illness and concurrent therapies. Advanced imaging modalities such as CT and MRI may aid in diagnosis but often incur delays because of logistical constraints, patient instability, and interobserver variability. Together with the marked etiological heterogeneity of NSTIs and diverse host factors, including diabetes, immunosuppression, and hematologic malignancy, these limitations substantially hinder timely diagnosis and accurate risk stratification in real-world clinical settings.

A visual summary of these interconnected challenges is presented in Figure 3, which outlines the multifactorial nature of diagnostic barriers in ICU-based NSTI management. These include clinical ambiguity, biomarker limitations, imaging constraints, microbial diversity, and global disparities in diagnostic capacity, especially in low-resource settings.

However, translation into routine ICU practice remains hindered by several barriers. These include the need for large-scale, multicenter prospective validation across diverse populations; integration with electronic medical records (EMRs) and decision-support systems (DSS); and ensuring affordability, usability, and sustainability in both high- and low-income health systems.

A structured roadmap to address these needs is proposed in Figure 4, outlining five progressive phases—from foundational registry building and biomarker discovery to model development,

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

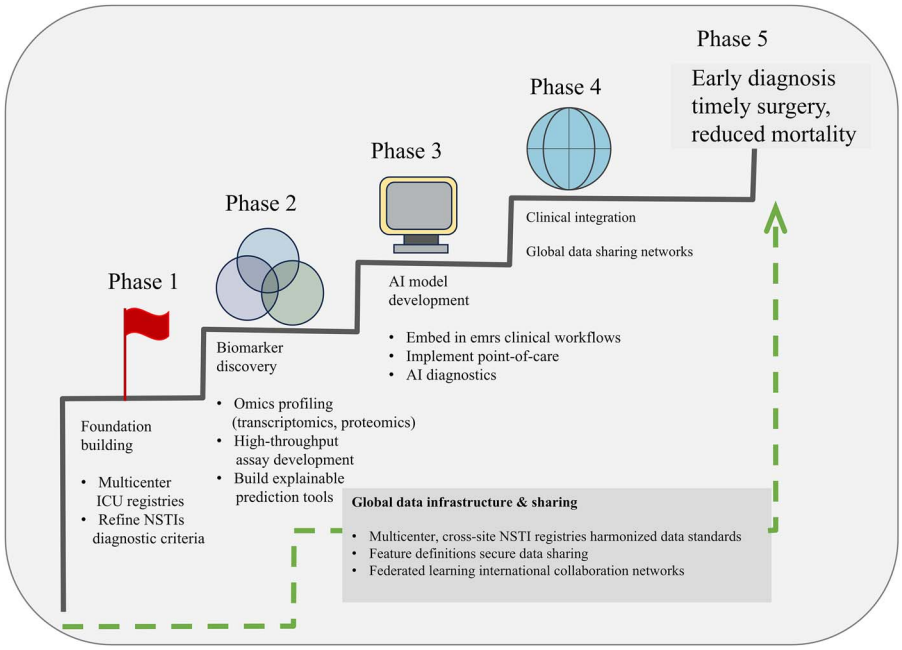


Figure 4 Translational roadmap toward precision NSTI diagnosis. A five-phase framework advancing NSTI diagnostics from ICU data foundations to global-scale, AI-enabled solutions aimed at improving early detection and reducing mortality. *NSTI* necrotizing soft tissue infection

clinical integration, and global equity-focused scaling. This translational pathway emphasizes both scientific rigor and clinical relevance, aiming to create adaptive systems that reflect ICU-specific diagnostic realities.

Conclusions

Despite ongoing advances in diagnostic methodologies, NSTIs continue to pose significant challenges in critical care settings. Traditional scoring systems such as the LRINEC score demonstrate considerable variability in sensitivity and specificity across diverse populations, limiting their utility, particularly among immunocompromised or comorbid patients. While imaging modalities and laboratory indices provide some diagnostic support, their practical application in the ICU is frequently limited by clinical instability and resource limitations. The emergence of multi-omics technologies—encompassing transcriptomics, proteomics, metabolomics, and immunomics—combined with ML algorithms offers a promising avenue for more accurate, timely, and individualized diagnosis. These integrative approaches enable the identification of pathogen-specific and host–response biomarkers that may facilitate early recognition and risk stratification. Moving forwards, large-scale prospective validation and seamless integration into clinical workflows—particularly DSS within electronic health records—will be essential to translate these innovations into improved outcomes. A paradigm shift toward data-driven, precision diagnostics represents a critical step in narrowing the current diagnostic gap and reducing the high morbidity and mortality associated with NSTIs.

Abbreviations

NSTI(s), necrotizing soft tissue infection(s); NF, necrotizing fasciitis; FG, Fournier's gangrene; GAS, Group A Streptococcus; MRSA, Methicillin-resistant *Staphylococcus aureus*; CT, computed tomography; MRI, magnetic resonance imaging; POCUS, point-of-care ultrasound; NIRS, near-infrared spectroscopy; LRINEC, Laboratory Risk Indicator for Necrotizing Fasciitis; m-LRINEC, Modified LRINEC (Wu *et al.*, 2021); MLRINEC, Modified LRINEC (lactate and liver disease); J-LRINEC, Japan-modified LRINEC; MRINEC, MRI-based LRINEC algorithm; MELD, Model for End-Stage Liver Disease; ΔMELD, Delta MELD (change in MELD); AMELD, adjusted MELD; SIARI, site, immunosuppression, age, renal function, inflammatory markers; LARINF, lactate, albumin, renal function, inflammatory markers; FGMI, Fournier's gangrene mortality index; NECROSIS score, NECROSIS score (Kim *et al.*, 2024); SII, Systemic immune–inflammation index; CCI, Charlson Comorbidity Index; AUC, area under the curve; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; DSS, decision-support system; SOFA, sequential organ failure assessment; HBO_2, hyperbaric oxygen therapy; SHAP, SHapley Additive exPlanations; ML, machine learning; AI, artificial intelligence; LightGBM, light gradient boosting machine; CRP/hs-CRP, C-reactive protein/high-sensitivity CRP; WBC, white blood cell (count); Hb, hemoglobin; Na, sodium; Cr, creatinine; Alb, albumin; eGFR, estimated glomerular filtration rate; CK, creatine kinase; PT, prothrombin time; INR, international normalized ratio; SBP, systolic blood pressure; NLR, neutrophil-to-lymphocyte ratio; PTX3, Pentraxin 3; PCT, procalcitonin; rRNA (16S rRNA), ribosomal RNA (16S ribosomal RNA); ADMA, asymmetric dimethylarginine; QTL, quantitative trait loci; VNTR, variable number tandem repeat; NLRP3, NOD-like receptor family pyrin domain containing 3; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-10, interleukin-10; TNF-α, tumor necrosis factor-alpha; STAT1, signal transducer and activator of transcription 1; CXCL9, C-X-C motif chemokine ligand 9; IL1R2, interleukin-1 receptor type 2; IL18R1, interleukin-18 receptor 1; speA/speG/speJ, streptococcal pyrogenic exotoxin A/G/J (genes); sagA, streptolysin S precursor (gene); speB, streptococcal cysteine protease (gene); spd, secreted DNase (gene); scfA/scfB, *Streptococcus pyogenes* core genome factors A/B

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

(genes); Dev/Val, development/validation; STI, surgically treated soft tissue infection; ICU, Intensive care unit

Author contributions

Zhongqiu Lu (Conceptualization, Writing—review & editing, Funding acquisition), Xiaolin Ji (Project administration, Writing—original draft), and Xinze Li (Investigation, Validation)

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Funding

This work was financially supported by the National Natural Science Foundation of China (No. 82272201), the Key Research and Development Program Project of Zhejiang Province (No. 2021C03072), the Zhejiang Clinovation Pride (CXTD202501043), the Key Clinical Specialty of Emergency Medicine in Zhejiang Province, the Zhejiang Provincial Interdisciplinary Innovation Team for the Diagnosis and Treatment of Sepsis in Traditional Chinese Medicine, and the provincial advantageous characteristic discipline of Wenzhou Medical University (clinical medicine).

Data availability

The datasets generated and/or analysed during this study are available from the corresponding author upon reasonable request.

References

1. Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL, Low CO. Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. *J Bone Joint Surg Am* 2003;85:1454–60. https://doi.org/10.2106/00004623-200308000-00005.
2. Hakkarainen TW, Kopari NM, Pham TN, Evans HL. Necrotizing soft tissue infections: review and current concepts in treatment, systems of care, and outcomes. *Curr Probl Surg* 2014;51:344–62. https://doi.org/10.1067/j.cpsurg.2014.06.001.
3. Stevens DL, Bryant AE. Necrotizing soft-tissue infections. *N Engl J Med* 2017;377:2253–65. https://doi.org/10.1056/NEJMra1600673.
4. Bhat SS, Pallavi HR, Koppolu S, Ahmed MM, Nair AU, Madhusudhanan D. *et al.* Enhancing early detection of necrotizing soft tissue infections: the role of the laboratory risk indicator for necrotizing fasciitis (LRINEC) score. *Cureus* 2024;16:e61620. https://doi.org/10.7759/cureus.61620.
5. McDermott J, Kao LS, Keeley JA, Grigorian A, Neville A, de Virgilio C. Necrotizing soft tissue infections: a review. *JAMA Surg* 2024;159:1308–15. https://doi.org/10.1001/jamasurg.2024.3365.
6. Pelletier J, Gottlieb M, Long B, Perkins JC Jr. Necrotizing soft tissue infections (NSTI): pearls and pitfalls for the emergency clinician. *J Emerg Med* 2022;62:480–91. https://doi.org/10.1016/j.jemermed.2021.12.012.
7. Zhao JC, Zhang BR, Shi K, Zhang X, Xie CH, Wang J, *et al.* Necrotizing soft tissue infection: clinical characteristics and outcomes at a reconstructive center in Jilin Province. *BMC Infect Dis* 2017;17:792. https://doi.org/10.1186/s12879-017-2907-6.
8. Neilly DW, Smith M, Woo A, Bateman V, Stevenson I. Necrotising fasciitis in the north east of Scotland: a 10-year retrospective review. *Ann R Coll Surg Engl* 2019;101:363–72. https://doi.org/10.1308/rcsann.2019.0013.
9. Wang JM, Lim HK. Necrotizing fasciitis: eight-year experience and literature review. *Braz J Infect Dis* 2014;18:137–43. https://doi.org/10.1016/j.bjid.2013.08.003.
10. Machado N. Necrotizing fasciitis: the importance of early diagnosis, prompt surgical debridement and adjuvant therapy. *N Am J Med Sci* 2011;3:107–18. https://doi.org/10.4297/najms.2011.3107.
11. Tessier JM, Sanders J, Sartelli M, Ulrych J, de Simone B, Grabowski J, *et al.* Necrotizing soft tissue infections: a focused review of pathophysiology, diagnosis, operative management, antimicrobial therapy, and Pediatrics. *Surg Infect* 2020;21:81–93. https://doi.org/10.1089/sur.2019.219.
12. Johansson L, Thulin P, Low DE, Norrby-Teglund A. Getting under the skin: the immunopathogenesis of Streptococcus pyogenes deep tissue infections. *Clin Infect Dis* 2010;51:58–65. https://doi.org/10.1086/653116.
13. Borschitz T, Schlicht S, Siegel E, Hanke E, von Stebut E. Improvement of a clinical score for necrotizing fasciitis: 'pain out of proportion' and high CRP levels aid the diagnosis. *PLoS One* 2015;10:e0132775. https://doi.org/10.1371/journal.pone.0132775.
14. Hefny AF, Eid HO, Al-Hussona M, Idris KM, Abu-Zidan FM. Necrotizing fasciitis: a challenging diagnosis. *Eur J Emerg Med* 2007;14:50–2. https://doi.org/10.1097/01.mej.0000228447.48276.7b.
15. van Stigt SF, de Vries J, Bijker JB, Mollen RMHG, Hekma EJ, Lemson SM, *et al.* Review of 58 patients with necrotizing fasciitis in the Netherlands. *World J Emerg Surg* 2016;11:21. https://doi.org/10.1186/s13017-016-0080-7.
16. Kariksiz M, Ates O. Treatment and clinical outcomes in lower extremity necrotizing soft tissue infection. *Eur J Trauma Emerg Surg* 2025;51:148. https://doi.org/10.1007/s00068-025-02835-5.
17. Bechar J, Sepehripour S, Hardwicke J, Filobbos G. Laboratory risk indicator for necrotising fasciitis (LRINEC) score for the assessment of early necrotising fasciitis: a systematic review of the literature. *Ann R Coll Surg Engl* 2017;99:341–6. https://doi.org/10.1308/rcsann.2017.0053.
18. Ronan D, Holt H, Utsi L, Arunachalam N, Tate D, Lamagni T, *et al.* Localised increase in necrotising fasciitis associated with a shift to monomicrobial aetiology, South Yorkshire,

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

England, 2023. *J Inf Secur* 2025;90:106505. https://doi.org/10.1016/j.jinf.2025.106505.
19. Asai N, Ohashi W, Kishino T, Sakanashi D, Shibata Y, Kato H, *et al.* The combined score of quick SOFA and the charlson comorbidity index could be a poor prognostic indicator for in-hospital mortality among patients with necrotizing fasciitis. *J Infect Chemother* 2021;27:919–23. https://doi.org/10.1016/j.jiac.2021.02.024.
20. Dhanasekara CS, Marschke B, Morris E, Kahathuduwa CN, Dissanaike S. Global patterns of necrotizing soft tissue infections: a systematic review and meta-analysis. *Surgery* 2021;170:1718–26. https://doi.org/10.1016/j.surg.2021.06.036.
21. Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (laboratory risk indicator for necrotizing fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med* 2004;32:1535–41. https://doi.org/10.1097/01.ccm.0000129486.35458.7d.
22. Henry R, Matsushima K, Etzel M, Henry RN, Golden A, Wong V, *et al.* Utility of the laboratory risk indicator for necrotizing fasciitis score: comorbid conditions do matter. *Surg Infect* 2021;22:797–802. https://doi.org/10.1089/sur.2020.398.
23. Abdullah M, McWilliams B, Khan SU. Reliability of the laboratory risk indicator in necrotising fasciitis (LRINEC) score. *Surgeon* 2019;17:309–18. https://doi.org/10.1016/j.surge.2018.08.001.
24. Johnson LJ, Crisologo PA, Sivaganesan S, Caldwell CC, Henning J. Evaluation of the laboratory risk indicator for necrotizing fasciitis (LRINEC) score for detecting necrotizing soft tissue infections in patients with diabetes and lower extremity infection. *Diabetes Res Clin Pract* 2021;171:108520. https://doi.org/10.1016/j.diabres.2020.108520.
25. Bennett M. Is early diagnosis of necrotizing fasciitis important? *ANZ J Surg* 2008;78:947–8. https://doi.org/10.1111/j.1445-2197.2008.04710.x.
26. Foo RM, Tung ML, Poon LM, Chan D, Smitasin N, Koh LP, *et al.* Necrotizing fasciitis in hematological patients: enterobacteriaceae predominance and limited utility of laboratory risk indicator for necrotizing fasciitis score. *Open Forum Infect Dis* 2015;2:ofv081. https://doi.org/10.1093/ofid/ofv081.
27. Rogers PJ, Lewis BM, Odak M, Bucher J. Spontaneous necrotizing fasciitis. *Cureus* 2020;12:e11880. https://doi.org/10.7759/cureus.11880.
28. Tan JH, Koh BT, Hong CC, Lim SH, Liang S, Chan GW, *et al.* A comparison of necrotising fasciitis in diabetics and non-diabetics: a review of 127 patients. *Bone Joint J* 2016;98-B:1563–8. https://doi.org/10.1302/0301-620X.98B11.37526.
29. Albasanz-Puig A, Rodriguez-Pardo D, Pigrau C, Lung M, Roldan E, Corona PS, *et al.* Necrotizing fasciitis in haematological patients: a different scenario. *Ann Hematol* 2020;99:1741–7. https://doi.org/10.1007/s00277-020-04061-y.
30. MacLeod CS, O'Neill HL, Shaalan R, Nagy J, Flett MM, Guthrie GJK, *et al.* 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. *Int J Surg* 2023;109:1561–72. https://doi.org/10.1097/JS9.0000000000000367.
31. Hansen MB, Rasmussen LS, Svensson M, Chakrakodi B, Bruun T, Madsen MB. *et al.* Association between cytokine response, the LRINEC score and outcome in patients with necrotising soft tissue infection: a multicentre, prospective study. *Sci Rep* 2017;7:42179. https://doi.org/10.1038/srep42179.
32. Wiggenhauser PS, Hoffmann TK. Comment on: "cervical necrotizing fasciitis-the value of the laboratory risk indicator for necrotizing fasciitis score as an indicative parameter". *J Oral Maxillofac Surg* 2016;74:1104–5. https://doi.org/10.1016/j.joms.2015.12.025.
33. Hsiao CT, Chang CP, Huang TY, Chen YC, Fann WC. Prospective validation of the laboratory risk indicator for necrotizing fasciitis (LRINEC) score for necrotizing fasciitis of the extremities. *PLoS One* 2020;15:e0227748. https://doi.org/10.1371/journal.pone.0227748.
34. Bair MJ, Chi H, Wang WS, Hsiao YC, Chiang RA, Chang KY. Necrotizing fasciitis in Southeast Taiwan: clinical features, microbiology, and prognosis. *Int J Infect Dis* 2009;13:255–60. https://doi.org/10.1016/j.ijid.2008.04.015.
35. Wu KH, Chang CP. Differentiating lower extremity necrotizing soft tissue infection from severe cellulitis by laboratory parameters and relevant history points. *Infect Drug Resist* 2021;Volume 14:3563–9. https://doi.org/10.2147/IDR.S327880.
36. Afzal M, Saccenti E, Madsen MB, Hansen MB, Hyldegaard O, Skrede S, *et al.* Integrated univariate, multivariate, and correlation-based network analyses reveal metabolite-specific effects on bacterial growth and biofilm formation in necrotizing soft tissue infections. *J Proteome Res* 2020;19:688–98. https://doi.org/10.1021/acs.jproteome.9b00565.
37. Hansen MB, Rasmussen LS, Garred P, Pilely K, Wahl AM, Perner A, *et al.* Associations of plasma nitrite, L-arginine and asymmetric dimethylarginine with morbidity and mortality in patients with necrotizing soft tissue infections. *Shock* 2018;49:667–74. https://doi.org/10.1097/SHK.0000000000000975.
38. Imohl M, Fitzner C, Perniciaro S, van der Linden M. Epidemiology and distribution of 10 superantigens among invasive Streptococcus pyogenes disease in Germany from 2009 to 2014. *PLoS One* 2017;12:e0180757. https://doi.org/10.1371/journal.pone.0180757.
39. Katz S, Suijker J, Hardt C, Madsen MB, Vries AMD, Pijpe A, *et al.* Decision support system and outcome prediction in a cohort of patients with necrotizing soft-tissue infections. *Int J Med Inform* 2022;167:104878. https://doi.org/10.1016/j.ijmedinf.2022.104878.
40. Jahagirdar S, Morris L, Benis N, Oppegaard O, Svenson M, Hyldegaard O, *et al.* Analysis of host-pathogen gene association networks reveals patient-specific response to streptococcal and polymicrobial necrotising soft tissue infections. *BMC Med* 2022;20:173. https://doi.org/10.1186/s12916-022-02355-8.
41. Shumba P, Mairpady Shambat S, Siemens N. The role of streptococcal and staphylococcal exotoxins and proteases in human necrotizing soft tissue infections. *Toxins (Basel)* 2019;11:332. https://doi.org/10.3390/toxins11060332.
42. Sarani B, Strong M, Pascual J, Schwab CW. Necrotizing fasciitis: current concepts and review of the literature. *J Am Coll Surg* 2009;208:279–88. https://doi.org/10.1016/j.jamcollsurg.2008.10.032.

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

43. Miller LG, Perdreau-Remington F, Rieg G, Mehdi S, Perlroth J, Bayer AS, *et al.* Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles. *N Engl J Med* 2005;352:1445–53. https://doi.org/10.1056/NEJMoa042683.
44. Giuliano A, Lewis F Jr, Hadley K, Blaisdell FW. Bacteriology of necrotizing fasciitis. *Am J Surg* 1977;134:52–7. https://doi.org/10.1016/0002-9610(77)90283-5.
45. Morgan MS. Diagnosis and management of necrotising fasciitis: a multiparametric approach. *J Hosp Infect* 2010;75:249–57. https://doi.org/10.1016/j.jhin.2010.01.028.
46. Chaudhry AA, Baker KS, Gould ES, Gupta R. Necrotizing fasciitis and its mimics: what radiologists need to know. *AJR Am J Roentgenol* 2015;204:128–39. https://doi.org/10.2214/AJR.14.12676.
47. Glass GE, Sheil F, Ruston JC, Butler PE. Necrotising soft tissue infection in a UK metropolitan population. *Ann R Coll Surg Engl* 2015;97:46–51. https://doi.org/10.1308/003588414X14055925058553.
48. Abad Hernandez MA. Soft-tissue infections. *Reumatol Clin* 2008;4:35–40. Infeccion de partes blandas. https://doi.org/10.1016/S1699-258X(08)76166-7.
49. Naamany E, Shiber S, Duskin-Bitan H, Yahav D, Bishara J, Sagy I. *et al.* Polymicrobial and monomicrobial necrotizing soft tissue infections: comparison of clinical, laboratory, radiological, and pathological hallmarks and prognosis. A retrospective analysis. *Trauma Surg Acute Care Open* 2021;6:e000745. https://doi.org/10.1136/tsaco-2021-000745.
50. Dehority W, Wang E, Vernon PS, Lee C, Perdreau-Remington F, Bradley J. Community-associated methicillin-resistant Staphylococcus aureus necrotizing fasciitis in a neonate. *Pediatr Infect Dis J* 2006;25:1080–1. https://doi.org/10.1097/01.inf.0000243158.25713.29.
51. Lee YT, Lin JC, Wang NC, Peng MY, Chang FY. Necrotizing fasciitis in a medical center in northern Taiwan: emergence of methicillin-resistant Staphylococcus aureus in the community. *J Microbiol Immunol Infect* 2007;40:335–41.
52. Gregory CJ, Okaro JO, Reingold A, Chai S, Herlihy R, Petit S, *et al.* Invasive group a streptococcal infections in 10 US states. *JAMA* 2025;333:1498–507. https://doi.org/10.1001/jama.2025.0910.
53. Bross MH, Soch K, Morales R, Mitchell RB. Vibrio vulnificus infection: diagnosis and treatment. *Am Fam Physician* 2007;76:539–44.
54. Goodell KH, Jordan MR, Graham R, Cassidy C, Nasraway SA. Rapidly advancing necrotizing fasciitis caused by Photobacterium (Vibrio) damsela: a hyperaggressive variant. *Crit Care Med* 2004;32:278–81. https://doi.org/10.1097/01.CCM.0000104920.01254.82.
55. Tsai YH, Huang KC, Shen SH, Hsu WH, Peng KT, Huang TJ. Microbiology and surgical indicators of necrotizing fasciitis in a tertiary hospital of Southwest Taiwan. *Int J Infect Dis* 2012;16:e159–65. https://doi.org/10.1016/j.ijid.2011.11.001.
56. Cheng NC, Tai HC, Chang SC, Chang CH, Lai HS. Necrotizing fasciitis in patients with diabetes mellitus: clinical characteristics and risk factors for mortality. *BMC Infect Dis* 2015;15:417. https://doi.org/10.1186/s12879-015-1144-0.
57. Hua C, Urbina T, Bosc R, Parks T, Sriskandan S, de Prost N, *et al.* Necrotising soft-tissue infections. *Lancet Infect Dis* 2023;23:e81–94. https://doi.org/10.1016/S1473-3099(22)00583-7.
58. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJC, Gorbach SL, *et al.* Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2014;59:e10–52. https://doi.org/10.1093/cid/ciu296.
59. Park KH, Jung SI, Jung YS, Shin JH, Hwang JH. Marine bacteria as a leading cause of necrotizing fasciitis in coastal areas of South Korea. *Am J Trop Med Hyg* 2009;80:646–50. https://doi.org/10.4269/ajtmh.2009.80.646.
60. Tsai YH, Huang TY, Kuo LT, Chuang PY, Hsiao CT, Huang KC. Comparison of surgical outcomes and predictors in patients with monomicrobial necrotizing fasciitis and sepsis caused by Vibrio vulnificus, Aeromonas hydrophila, and Aeromonas sobria. *Surg Infect* 2022;23:288–97. https://doi.org/10.1089/sur.2021.337.
61. Becker DK, Roder M, Wagenhauser J, Eichberger S, Herten M, Dudda M. Necrotizing fasciitis that led to unexpected and fulminant deterioration in less than 24 hours: a case report. *J Int Med Res* 2024;52:3000605241290480. https://doi.org/10.1177/03000605241290480.
62. Cheng NC, Cheng Y, Tai HC, Chien KL, Wang SH, Chen YH, *et al.* High mortality risk of type III monomicrobial gram-negative necrotizing fasciitis: the role of extraintestinal pathogenic Escherichia coli (ExPEC) and Klebsiella pneumoniae. *Int J Infect Dis* 2023;132:64–71. https://doi.org/10.1016/j.ijid.2023.04.390.
63. Strom MS, Paranjpye RN. Epidemiology and pathogenesis of Vibrio vulnificus. *Microbes Infect* 2000;2:177–88. https://doi.org/10.1016/s1286-4579(00)00270-7.
64. Kuehl R, Tschudin-Sutter S, Siegemund M, Marsch S, Battegay M, Wetterauer C, *et al.* High mortality of non-Fournier necrotizing fasciitis with Enterobacteriales: time to rethink classification? *Clin Infect Dis* 2019;69:147–50. https://doi.org/10.1093/cid/ciy1011.
65. Park SY, Yu SN, Lee EJ, Kim T, Jeon MH, Choo EJ, *et al.* Monomicrobial gram-negative necrotizing fasciitis: an uncommon but fatal syndrome. *Diagn Microbiol Infect Dis* 2019;94:183–7. https://doi.org/10.1016/j.diagmicrobio.2018.12.013.
66. Cook DA, Heiner JP, Rao VK. Necrotizing candidal fasciitis following hip surgery. *Orthopedics* 1990;13:768–70. https://doi.org/10.3928/0147-7447-19900701-14.
67. Jain D, Kumar Y, Vasishta RK, Rajesh L, Pattari SK, Chakrabarti A. Zygomycotic necrotizing fasciitis in immunocompetent patients: a series of 18 cases. *Mod Pathol* 2006;19:1221–6. https://doi.org/10.1038/modpathol.3800639.
68. Tedesco S, Di Grezia M, Tropeano G, Altieri G, Brisinda G. Necrotizing soft tissue infections: a surgical narrative review. *Updat Surg* 2025;77:1239–51. https://doi.org/10.1007/s13304-025-02222-0.
69. Ezemma O, Korman AM, Wang HE, Kaffenberger B. Diagnostic methods for the confirmation of non-purulent cellulitis: a review. *Arch Dermatol Res* 2023;315:2519–27. https://doi.org/10.1007/s00403-023-02658-7.
70. Kirven RM, Wang H, Kaffenberger BH. Moving goalposts: a call for diagnostic advancements and a consensus gold-standard in patients with cellulitis to improve research rigor.

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

J Am Coll Emerg Physicians Open 2023;4:e12970. https://doi.org/10.1002/emp2.12970.
71. Goldenberg M, Wang H, Walker T, Kaffenberger BH. Clinical and immunologic differences in cellulitis vs. pseudocellulitis. *Expert Rev Clin Immunol* 2021;17:1003–13. https://doi.org/10.1080/1744666X.2021.1953982.
72. Boettler MA, Kaffenberger BH, Chung CG. Cellulitis: a review of current practice guidelines and differentiation from Pseudocellulitis. *Am J Clin Dermatol* 2022;23:153–65. https://doi.org/10.1007/s40257-021-00659-8.
73. Lause M, Hansen E, Libson K, Pettit C, Himed S, Rismiller KP, *et al.* The effect of histopathologic analysis and tissue cultures on inpatient management of cellulitis: a randomized control trial. *Arch Dermatol Res* 2024;316:482. https://doi.org/10.1007/s00403-024-03224-5.
74. Nusbaum KB, Boettler M, Korman AM, Alavi A, Alloo A, Dissemond J, *et al.* Subjective assessments in pyoderma gangrenosum diagnostic frameworks undermine framework agreement. *Int J Dermatol* 2024;63:e67–9. https://doi.org/10.1111/ijd.16952.
75. Hamann CR, Chung C, Kaffenberger BH. Pyoderma gangrenosum associated with dulaglutide therapy. *Int J Dermatol* 2019;58:1202–4. https://doi.org/10.1111/ijd.14272.
76. Hoffman KP, Shearer S, Chung C, Kaffenberger JA, Kaffenberger BH. Clinical and therapeutic overlap of pyoderma gangrenosum, cutaneous small vessel vasculitis, and immunoglobulin A. *Int J Dermatol* 2020;59:e286–8. https://doi.org/10.1111/ijd.14841.
77. Demirdover C, Geyik A, Vayvada H. Necrotising fasciitis or pyoderma gangrenosum: a fatal dilemma. *Int Wound J* 2019;16:1347–53. https://doi.org/10.1111/iwj.13196.
78. Heath MS, Ortega-Loayza AG. Insights into the pathogenesis of Sweet's syndrome. *Front Immunol* 2019;10:414. https://doi.org/10.3389/fimmu.2019.00414.
79. Elbendary A, Abdel-Halim MRE, Ragab G. Updates in cutaneous manifestations of systemic vasculitis. *Curr Opin Rheumatol* 2022;34:25–32. https://doi.org/10.1097/BOR.0000000000000847.
80. Gallardo MA, Yan A, Korman AM, Chung C, Kaffenberger BH. Unmet needs in the study of cellulitis: a response to Salle et al's "challenges and limitations of teledermatology for skin and soft-tissue infections: a real-world study of an expert center". *J Am Acad Dermatol* 2023;88:e307–8. https://doi.org/10.1016/j.jaad.2023.02.039.
81. Hayeri MR, Ziai P, Shehata ML, Teytelboym OM, Huang BK. Soft-tissue infections and their imaging mimics: from cellulitis to necrotizing fasciitis. *Radiographics* 2016;36:1888–910. https://doi.org/10.1148/rg.2016160068.
82. Holland MJ. Application of the laboratory risk indicator in necrotising fasciitis (LRINEC) score to patients in a tropical tertiary referral Centre. *Anaesth Intensive Care* 2009;37:588–92. https://doi.org/10.1177/0310057X0903700416.
83. Al-Hindawi A, McGhee J, Lockey J, Vizcaychipi M. Validation of the laboratory risk indicator for necrotising fasciitis scoring system (LRINEC) in a northern European population. *J Plast Reconstr Aesthet Surg* 2017;70:141–3. https://doi.org/10.1016/j.bjps.2016.05.014.
84. Syed A, Alvin T, Fazrina A, Abdul R. Determining if positive predictive value using laboratory risk indicator for necrotising fasciitis is applicable in Malaysian patients with necrotising fasciitis. *Malays Orthop J* 2017;11:36–9. https://doi.org/10.5704/MOJ.1707.005.
85. Neeki MM, Dong F, Au C, Toy J, Khoshab N, Lee C, *et al.* Evaluating the laboratory risk indicator to differentiate cellulitis from necrotizing fasciitis in the emergency department. *West J Emerg Med* 2017;18:684–9. https://doi.org/10.5811/westjem.2017.3.33607.
86. Narasimhan V, Ooi G, Weidlich S, Carson P. Laboratory risk indicator for necrotizing fasciitis score for early diagnosis of necrotizing fasciitis in Darwin. *ANZ J Surg* 2018;88:E45–9. https://doi.org/10.1111/ans.13895.
87. Tsai YH, Hsu RW, Huang KC, Huang TJ. Laboratory indicators for early detection and surgical treatment of vibrio necrotizing fasciitis. *Clin Orthop Relat Res* 2010;468:2230–7. https://doi.org/10.1007/s11999-010-1311-y.
88. Karnuta J, Featherall J, Lawrenz J, Gordon J, Golubovsky J, Thomas J, *et al.* What demographic and clinical factors are associated with In-hospital mortality in patients with necrotizing fasciitis? *Clin Orthop Relat Res* 2020;478:1770–9. https://doi.org/10.1097/CORR.0000000000001187.
89. Breidung D, Malsagova AT, Barth AA, Megas IF, Billner M, Hitzl W, *et al.* Diagnostic and prognostic value of the laboratory risk indicator for necrotising fasciitis (LRINEC) based on an 18 years' experience. *J Plast Reconstr Aesthet Surg* 2023;77:228–35. https://doi.org/10.1016/j.bjps.2022.11.061.
90. Jegathesan T, Ho SWL, Tham SYY, Ang MLT. Predictors of clinical outcomes in necrotizing fasciitis: a ten year study. *Int Orthop* 2025;49:2047–54. https://doi.org/10.1007/s00264-025-06608-y.
91. Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: diagnosis and management. *Clin Infect Dis* 2007;44:705–10. https://doi.org/10.1086/511638.
92. Lunar J, Ranketi SS, Owino B, Oloo M, Parker RK. Necrotizing fasciitis: a predictable burden in rural Kenya. *World J Surg* 2020;44:2919–26. https://doi.org/10.1007/s00268-020-05581-4.
93. Horn DL, Shen J, Roberts E, Wang TN, Li KS, O'Keefe GE, *et al.* Predictors of mortality, limb loss, and discharge disposition at admission among patients with necrotizing skin and soft tissue infections. *J Trauma Acute Care Surg* 2020;89:186–91. https://doi.org/10.1097/TA.0000000000002636.
94. Wu H, Liu S, Li C, Song Z. Modified laboratory risk indicator for necrotizing fasciitis (m-LRINEC) score system in diagnosing necrotizing fasciitis: a nested case-control study. *Infect Drug Resist* 2021;14:2105–12. https://doi.org/10.2147/IDR.S313321.
95. Misiakos EP, Bagias G, Papadopoulos I, Danias N, Patapis P, Machairas N, *et al.* Early diagnosis and surgical treatment for necrotizing fasciitis: a multicenter study. *Front Surg* 2017;4:5. https://doi.org/10.3389/fsurg.2017.00005.
96. Bilton BD, Zibari GB, McMillan RW, Aultman DF, Dunn G, McDonald JC. Aggressive surgical management of necrotizing fasciitis serves to decrease mortality: a retrospective study. *Am Surg* 1998;64:397–400. discussion 400-1.
97. Tarricone A, Mata K, Gee A, Axman W, Buricea C, Mandato MG, *et al.* A systematic review and meta-analysis of the effectiveness of LRINEC score for predicting upper and lower extremity necrotizing fasciitis. *J Foot Ankle Surg* 2022;61:384–9. https://doi.org/10.1053/j.jfas.2021.09.015.

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

98. Quah GS, Cheng Q, Prabhu K, Edye MB. Necrotising soft tissue infection in western Sydney: an 8-year experience. *ANZ J Surg* 2021;91:1813–8. https://doi.org/10.1111/ans.16961.
99. Hosty J, Cheema A, Magdum AA. Necrotising fasciitis: clinical judgement and early multidisciplinary collaboration is the key. *Age Ageing* 2022;51:afab197. https://doi.org/10.1093/ageing/afab197.
100. Wu PH, Wu KH, Hsiao CT, Wu SR, Chang CP. Utility of modified laboratory risk indicator for necrotizing fasciitis (MLRINEC) score in distinguishing necrotizing from non-necrotizing soft tissue infections. *World J Emerg Surg* 2021;16:26. https://doi.org/10.1186/s13017-021-00373-0.
101. Huang KC, Tsai YH, Huang KC, Lee MS. Model for end-stage liver disease (MELD) score as a predictor and monitor of mortality in patients with Vibrio vulnificus necrotizing skin and soft tissue infections. *PLoS Negl Trop Dis* 2015;9:e0003720. https://doi:10.1371/journal.pntd.0003720.
102. Cribb BI, Wang MTM, Kulasegaran S, Gamble GD, MacCormick AD. The SIARI score: a novel decision support tool outperforms LRINEC score in necrotizing fasciitis. *World J Surg* 2019;43:2393–400. https://doi.org/10.1007/s00268-019-05061-4.
103. Kim MC, Kim S, Cho EB, Lee GY, Choi SH, Kim SO, *et al.* Utility of magnetic resonance imaging for differentiating necrotizing fasciitis from severe cellulitis: a magnetic resonance indicator for necrotizing fasciitis (MRINEC) algorithm. *J Clin Med* 2020;9:3040. https://doi.org/10.3390/jcm9093040.
104. Breidung D, Grieb G, Malsagova AT, Barth AA, Billner M, Hitzl W, *et al.* Time is fascia: laboratory and anamnestic risk indicators for necrotizing fasciitis. *Surg Infect* 2022;23:747–53. https://doi.org/10.1089/sur.2022.222.
105. Yönder H, Celik M, Berhuni MS, Genç AC, Elkan H, Tatlı F, *et al.* Fournier's gangrene mortality index (FGMI): a new scoring system for predicting Fournier's gangrene mortality. *Diagnostics (Basel)* 2024;14:2732. https://doi.org/10.3390/diagnostics14232732.
106. Kim DY, Lavasile A, Kaji AH, Nahmias J, Grigorian A, Mukherjee K, *et al.* Prospective derivation and validation of a necrotizing soft tissue infections score: an EASTmulticenter trial. *J Trauma Acute Care Surg* 2024;97:910–7. https://doi.org/10.1097/TA.0000000000004374.
107. Norimatsu Y, Fukasawa T, Ohno Y, Norimatsu Y, Matsuda KM, Hisamoto T, *et al.* Validation of laboratory risk indicator for necrotizing fasciitis (LRINEC) score and establishment of novel score in Japanese patients with necrotizing fasciitis (J-LRINEC score). *J Dermatol* 2025;52:439–44. https://doi.org/10.1111/1346-8138.17663.
108. Bolat F, Keyif MF, Sit M, Catal O, Ozer B, Erkol MH. Don't waste time with scoring systems to predict mortality in Fournier's Gangrene, regulate blood sugar, and defy death! *Ulus Travma Acil Cerrahi Derg* May 2025;31:472–9. Fournier Gangreni'nde mortaliteyi tahmin etmek icin puanlama sistemleriyle vakit kaybetmeyin, kan sekerini duzenleyin ve olume meydan okuyun! https://doi:10.14744/tjtes.2025.40921.
109. Cen H, Jin R, Yin J, Wang X. Risk factors for predicting mortality and amputation of patients with necrotizing soft-tissue infections: retrospective analysis of 111 cases from a single medical center. *Emerg Med Int* 2023;2023:1–12. https://doi.org/10.1155/2023/6316896.
110. Ture Z, Unuvar GK, Esmaoglu A, Ulu-Kilic A, Coruh A, Doganay M. Severe and complicated soft tissue infections: a single-centre case series. *J Wound Care* 2023;32:492–9. https://doi.org/10.12968/jowc.2023.32.8.492.
111. Celik M, Ciftci MU, Celik S, Öztürk V, Bayrak A, Duramaz A, *et al.* Can the systemic immune-inflammation index (SII) and Charlson comorbidity index (CCI) be used to predict mortality in patients with necrotizing fasciitis? *Int Orthop* 2024;48:1707–13. https://doi.org/10.1007/s00264-024-06190-9.
112. Ling XW, Lin K, Jiang XQ, Wu Q, Liu ZJ, Li S, *et al.* International normalised ratio as an independent predictor of mortality in limb necrotising fasciitis with sepsis. *Ann R Coll Surg Engl* 2021;103:35–40. https://doi.org/10.1308/rcsann.2020.0189.
113. Huang TY, Peng KT, Hsiao CT, Fann WC, Tsai YH, Li YY, *et al.* Predictors for gram-negative monomicrobial necrotizing fasciitis in southern Taiwan. *BMC Infect Dis* 2020;20:60. https://doi.org/10.1186/s12879-020-4796-3.
114. Huang TY, Peng KT, Hsu WH, Hung CH, Chuang FY, Tsai YH. Independent predictors of mortality for Aeromonas necrotizing fasciitis of limbs: an 18-year retrospective study. *Sci Rep* 2020;10:7716. https://doi.org/10.1038/s41598-020-64741-7.
115. Carbonetti F, Cremona A, Carusi V, Guidi M, Iannicelli E, di Girolamo M, *et al.* The role of contrast enhanced computed tomography in the diagnosis of necrotizing fasciitis and comparison with the laboratory risk indicator for necrotizing fasciitis (LRINEC). *Radiol Med* 2016;121:106–21. https://doi.org/10.1007/s11547-015-0575-4.
116. Bruls RJM, Kwee RM. CT in necrotizing soft tissue infection: diagnostic criteria and comparison with LRINEC score. *Eur Radiol* 2021;31:8536–41. https://doi.org/10.1007/s00330-021-08005-6.
117. Burke CE, Maley OR, Mancini B, Sardesai S, Montgomery AB, King TS, *et al.* Factors associated with positive findings of deep infection on computed tomography among patients with extremity cellulitis. *Diagnosis (Berl)* 2025;12:413–23. https://doi.org/10.1515/dx-2024-0156.
118. Medikonda E, Patil A, Muchchandi R, Kotennavar M, Jaju PP, Rathod S, *et al.* A study on the accuracy of point-of-care ultrasound in the diagnosis and management of necrotizing fasciitis. *Cureus* 2025;17:e83814. https://doi.org/10.7759/cureus.83814.
119. Oi M, Maruhashi T, Asari Y. Efficacy of near-infrared spectroscopy in diagnosing skin and soft tissue infections: a single-center retrospective study. *Acute Med Surg* 2025;12:e70041. https://doi.org/10.1002/ams2.70041.
120. Hirose Y, Yamaguchi M, Okuzaki D, Motooka D, Hamamoto H, Hanada T, *et al.* Streptococcus pyogenes transcriptome changes in the inflammatory environment of necrotizing fasciitis. *Appl Environ Microbiol* 2019;85(21):e01428-19. https://doi.org/10.1128/AEM.01428-19.
121. Valderrama JA, Riestra AM, Gao NJ, LaRock CN, Gupta N, Ali SR, *et al.* Group a streptococcal M protein activates the NLRP3 inflammasome. *Nat Microbiol* 2017;2:1425–34. https://doi.org/10.1038/s41564-017-0005-6.
122. Vu HM, Moran TE, Liang Z, Bao YJ, Carles PG, Keane JC, *et al.* Group a streptococcus remains viable inside fibrin clots

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026

and gains access to human plasminogen for subsequent fibrinolysis and dissemination. *Microbiol Spectrum* 2025; 13:e0260724. https://doi.org/10.1128/spectrum.02607-24.

123. Eraso JM, Olsen RJ, Beres SB, Kachroo P, Porter AR, Nasser W, *et al.* Genomic landscape of Intrahost variation in group a streptococcus: repeated and abundant mutational inactivation of the fabT gene encoding a regulator of fatty acid synthesis. *Infect Immun* 2016;84:3268–81. https://doi.org/10.1128/IAI.00608-16.
124. Zhu L, Olsen RJ, Horstmann N, Shelburne SA, Fan J, Hu Y, *et al.* Intergenic variable-number tandem-repeat polymorphism upstream of rocA alters toxin production and enhances virulence in Streptococcus pyogenes. *Infect Immun* 2016;84:2086–93. https://doi.org/10.1128/IAI.00258-16.
125. Aswani V, Najar F, Pantrangi M, Mau B, Schwan WR, Shukla SK. Virulence factor landscape of a Staphylococcus aureus sequence type 45 strain, MCRF184. *BMC Genomics* 2019;20:123. https://doi.org/10.1186/s12864-018-5394-2.
126. Adachi S, Takahashi T, Minami K, Kurabayashi H, Inoue H, Yonekawa C, *et al.* Predictors of fatal outcome after severe necrotizing fasciitis: retrospective analysis in a tertiary hospital for 20 years. *J Orthop Sci* 2021;26:494–9. https://doi.org/10.1016/j.jos.2020.04.007.
127. Liu S, Zhang YL, Zhang LY, Zhao GJ, Lu ZQ. FCGR2C: an emerging immune gene for predicting sepsis outcome. *Front Immunol* 2022;13:1028785. https://doi.org/10.3389/fimmu.2022.1028785.
128. Kishino T, Asai N, Ohashi W, Sakanashi D, Kato H, Shiota A, *et al.* Usefulness of serum procalcitonin for necrotizing fasciitis as an early diagnostic tool. *J Infect Chemother* 2021; 27:787–93. https://doi.org/10.1016/j.jiac.2021.01.002.
129. Kusumoto J, Iwata E, Huang W, Takata N, Tachibana A, Akashi M. Hematologic and inflammatory parameters for determining severity of odontogenic infections at admission: a retrospective study. *BMC Infect Dis* 2022;22:931. https://doi.org/10.1186/s12879-022-07934-x.
130. Zhu JL, Gao HJ, Yin ZT. The CRP/PAB ratio outperforms the LRINEC score in early diagnosis of Fournier's gangrene. *Surg Pract Sci* 2024;19:100267. https://doi.org/10.1016/j.sipas.2024.100267.
131. Hansen MB. Biomarkers of necrotising soft tissue infections aspects of the innate immune response. *Dan Med J* 2017;64:B5396.
132. Chella Krishnan K, Mukundan S, Alagarsamy J, Hur J, Nookala S, Siemens N, *et al.* Genetic architecture of group a streptococcal necrotizing soft tissue infections in the mouse. *PLoS Pathog* 2016;12:e1005732. https://doi.org/10.1371/journal.ppat.1005732.
133. LaRock DL, Russell R, Johnson AF, Wilde S, LaRock CN. Group a streptococcus infection of the nasopharynx requires Proinflammatory Signaling through the Interleukin-1 receptor. *Infect Immun* 2020;88:e00356-20. https://doi.org/10.1128/IAI.00356-20.
134. Saijo Y, Ono S, Akiyama G, Sugii M, Kodama Y, Nukaga S, *et al.* The discrepancy between white blood cell and C-reactive protein levels in group a streptococcal necrotizing soft-tissue infections. *Plast Reconstr Surg Glob Open* 2025;13:e6917. https://doi.org/10.1097/GOX.0000000000006917.
135. Palma, Medina LM, Rath E, Jahagirdar S, Bruun T, Madsen MB, Strålin K, *et al.* Discriminatory plasma biomarkers predict specific clinical phenotypes of necrotizing soft-tissue infections. *J Clin Invest* 2021;131:e149523. https://doi.org/10.1172/JCI149523.
136. Bergsten H, Madsen MB, Bergey F, Hyldegaard O, Skrede S, Arnell P, *et al.* Correlation between immunoglobulin dose administered and plasma neutralization of streptococcal superantigens in patients with necrotizing soft tissue infections. *Clin Infect Dis* 2020;71:1772–5. https://doi.org/10.1093/cid/ciaa022.
137. Johnson SR, Benvenuti T, Nian H, Thomson IP, Baldwin K, Obremskey WT, *et al.* Measures of admission immunocoagulopathy as an indicator for in-hospital mortality in patients with necrotizing fasciitis: a retrospective study. *JB JS Open Access* 2023;8. https://doi.org/10.2106/JBJS.OA.22.00106.
138. Le Breton Y, Belew AT, Freiberg JA, Sundar GS, Islam E, Lieberman J, *et al.* Genome-wide discovery of novel M1T1 group a streptococcal determinants important for fitness and virulence during soft-tissue infection. *PLoS Pathog* 2017;13:e1006584. https://doi.org/10.1371/journal.ppat.1006584.
139. Vinkel J, Rib L, Buil A, Hedetoft M, Hyldegaard O. Investigating the effects of hyperbaric oxygen treatment in necrotizing soft tissue infection with transcriptomics and machine learning (the HBOmic study): protocol for a prospective cohort study with data validation. *JMIR Res Protoc* 2022;11:e39252. https://doi.org/10.2196/39252.
140. Vinkel J, Buil A, Hyldegaard O. Blood from septic patients with necrotising soft tissue infection treated with hyperbaric oxygen reveal different gene expression patterns compared to standard treatment. *BMC Med Genet* 2025;18:12. https://doi.org/10.1186/s12920-024-02075-3.
141. Chang CP, Wu KH. Machine learning approach to classify Vibrio vulnificus necrotizing fasciitis, non-vibrio necrotizing fasciitis and cellulitis. *Infect Drug Resist* 2024;17:5513–21. https://doi.org/10.2147/IDR.S487893.
142. Chang CP, Lin CJ, Fann WC, Hsieh CH. Identifying necrotizing soft tissue infection using infectious fluid analysis and clinical parameters based on machine learning algorithms. *Heliyon* 2024;10:e29578. https://doi.org/10.1016/j.heliyon.2024.e29578.
143. Saccenti E, Svensson M. Systems biology and biomarkers in necrotizing soft tissue infections. *Adv Exp Med Biol* 2020;1294:167–86. https://doi.org/10.1007/978-3-030-57616-5_11.
144. Zhou L, Li H, Luo G, the CANF experts group representing the Chinese Burn Association, Editorial Board of the Chinese Journal of Burns and Wounds, Burn Medicine Branch of China International Exchange and Promotion Association for Medical and Healthcare. Consensus on the diagnosis and treatment of adult necrotizing fasciitis (2025 edition). *Burns Trauma* 2025;13:tkaf031. https://doi.org/10.1093/burnst/tkaf031.

© The Author(s) 2026. Published by Oxford University Press. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.
Burns & Trauma, 2026, 14, tkag028
https://doi.org/10.1093/burnst/tkag028
Review

Downloaded from academic.oup.com/burnstrauma/article/doi/10.1093/burnst/tkag028/8653883 by guest on 12 October 2026