

Introduction

Severe soft tissue infections (SSTIs) are progressive, life-threatening infections of skin, subcutaneous tissue, fascia or muscle (1). They are characterised by rapid clinical deterioration and require emergency surgical debridement for source control, combined with broad-spectrum antimicrobial therapy and organ support if necessary. SSTIs of the limbs including necrotising fasciitis are associated with high early mortality (1).

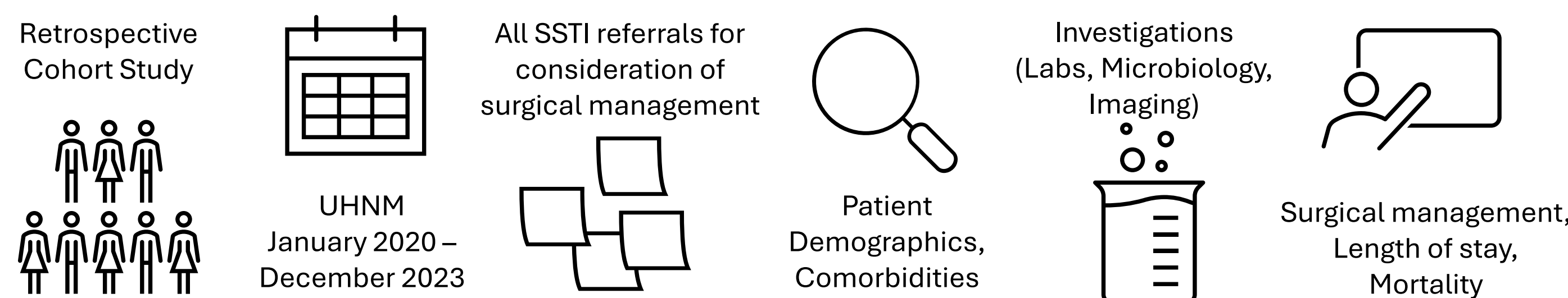
SSTIs can be mono- or poly-microbial; necrotising infections commonly involve Group A streptococcus as the cultured organism (2). Severe presentations are consistently associated with multimorbidity and disease processes such as diabetes mellitus, peripheral vascular disease, immunosuppression and intravenous substance use (2,3).

Diagnosing SSTIs is predominantly based on clinical judgement of the symptomatic burden, and rate of progression, supported by biochemical investigations and imaging (1,2). Emphasis is often placed on surgical timing; however, physiological drivers of early death and high-risk clinical phenotypes remain poorly defined.

Laboratory Risk Indicator for Necrotising Fasciitis (LRINEC) score was developed in the early 2000s to differentiate necrotising soft-tissue infections (NSTIs) from non-necrotising presentations (4). The score has consistently been challenged regarding low sensitivity for this purpose (5).

This study aimed to identify biochemical and clinical predictors of mortality and to characterise high-risk phenotypes to inform management and escalation decisions.

Materials and Methods



A retrospective cohort study was undertaken at University Hospitals of North Midlands NHS Trust between January 2020 and December 2023. Electronic patient records were evaluated for all referrals of suspected SSTIs and NSTIs.

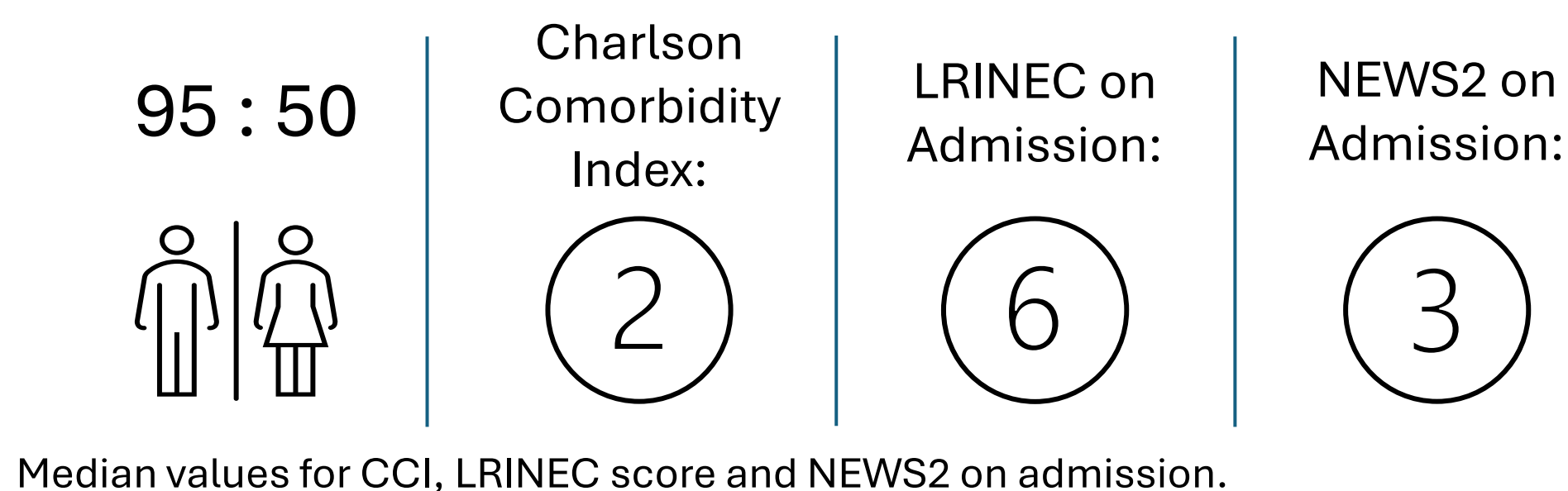
Patients were stratified by mortality timing into the following cohorts:

- Early Mortality (within 72 hours of admission)
- Late Mortality (between 72 hours up to 28 days)
- Survivors (beyond 28 days)

Comparative analyses were conducted using Mann-Whitney U and chi-square tests. Unsupervised machine learning (K-means clustering) identified underlying clinical phenotypes associated with early mortality. Analyses were performed in SPSS v31.0, with statistical significance set at $p < 0.05$.

Results

Cohort Overview



Surgical vs Medical Management

145 Patients	Surgical Management: 43	Early Mortality (<72 hours): 2 (4.7%) 28-day Mortality: 4 (9.4%)
	Medical Management: 102	Early Mortality (<72 hours): 5 (4.9%) 28-day Mortality: 15 (14.7%)

Figure 1: Cohort breakdown by management approach and mortality.

Clustering

Principal Component Analysis (PCA) and K-Means Clustering were used to determine whether patients could be grouped based on demographics and physiological status at presentation. Two distinct patient “phenotypes” were identified within the data set referred to as “Cluster 0” and “Cluster 1”.

Feature	Cluster 0 (Fit/Low-Risk)	Cluster 1 (Frail/High-Risk)
Primary Drivers	↓Inflammatory Markers Normal Renal Function	↑Creatinine, ↑Urea, ↑CRP
Metabolic State	Normal Electrolytes	↓eGFR, ↓Sodium
Prevalence	63% of Patients	37% of Patients
Mean Age	53 Years	68 Years
Comorbidity (CCI)	Low (1.97)	High (4.22)
LRINEC Score	4.3 (Low-Risk)	7.6 (High-Risk)
28-Day Mortality	4.4%	27.8%
Surgery Rate	31.9%	25.9%

Table 1: Comparison of clinical phenotypes identified by unsupervised clustering.

Despite having significantly higher LRINEC scores and mortality rates, Cluster 1 patients were less likely to undergo surgery. This suggests that “High-Risk” patients are managed more conservatively, perhaps due to perceived surgical futility or significant perioperative risk in older, multimorbid people.

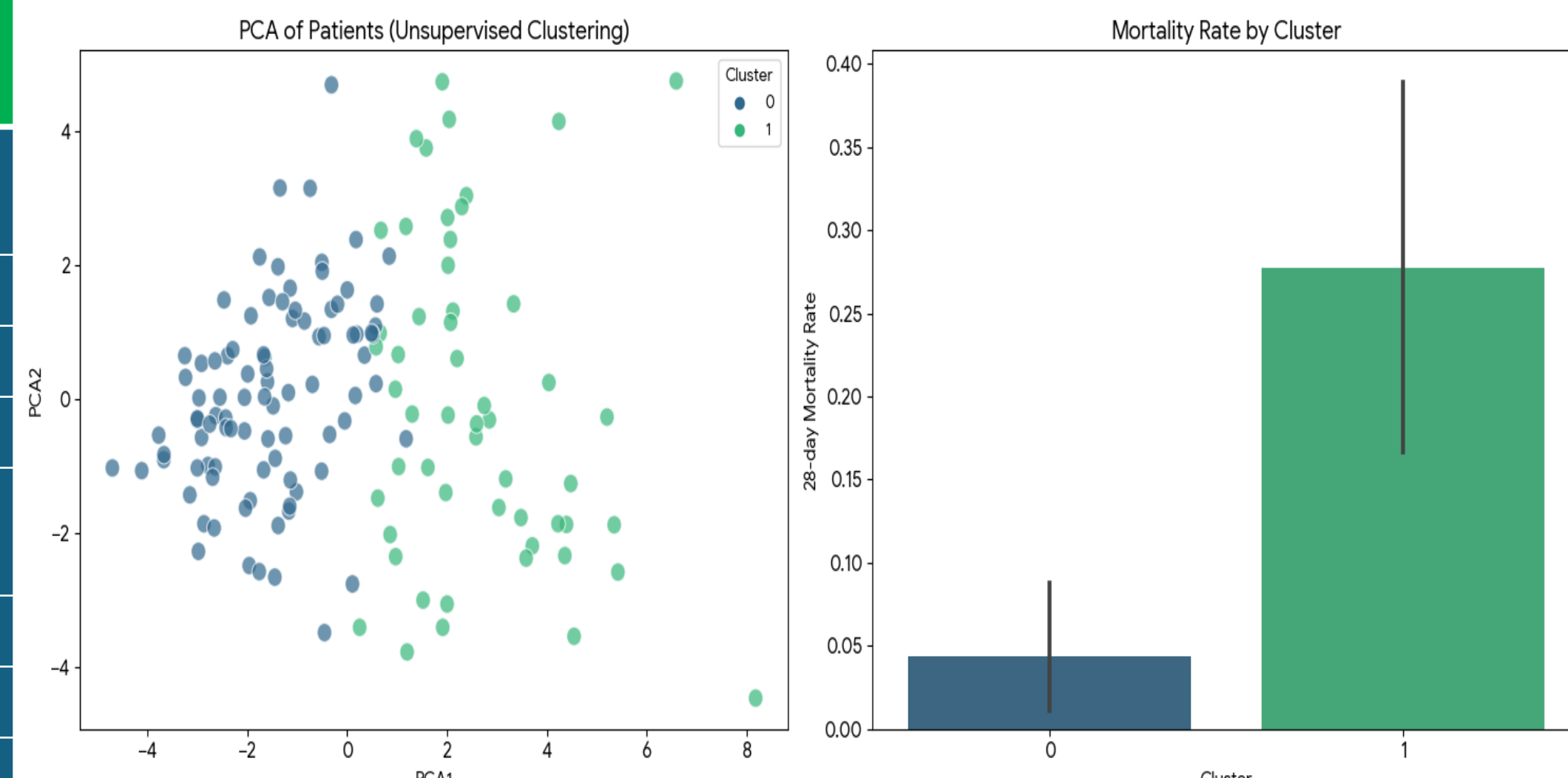
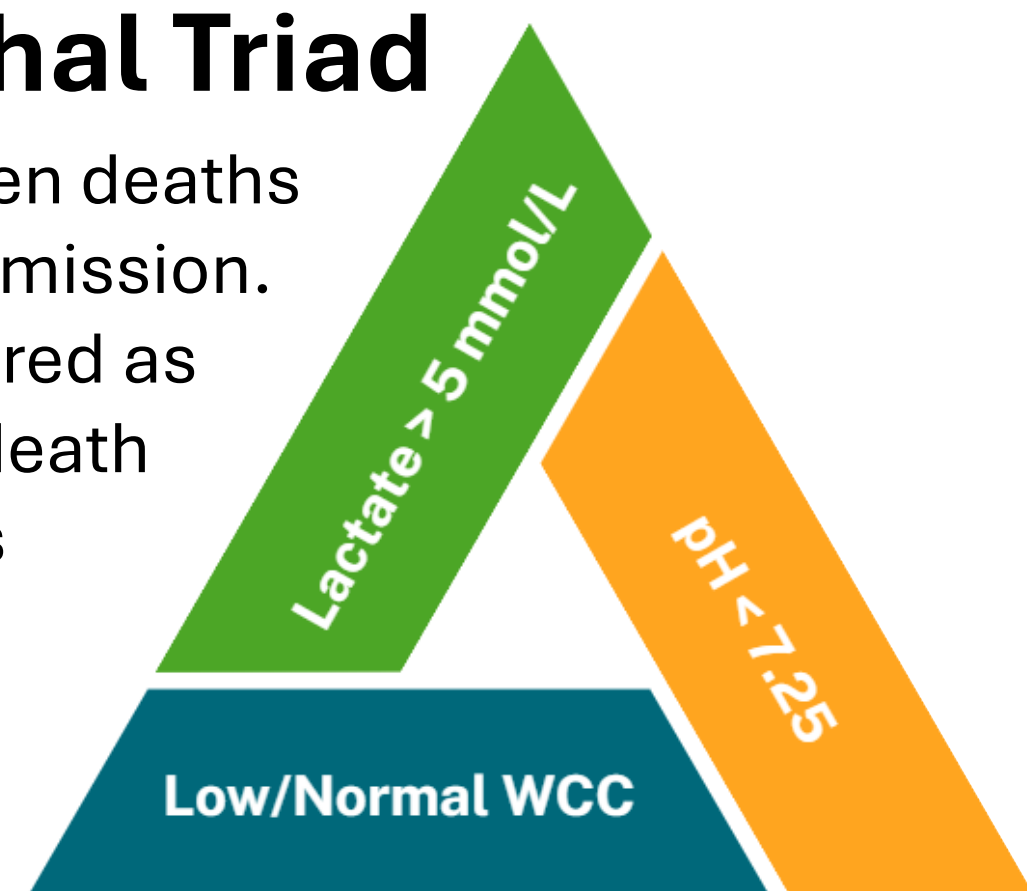


Figure 2: Unsupervised machine learning identifies two distinct patient phenotypes with differing mortality risk.

The Lethal Triad

Seven out of the total nineteen deaths occurred within 3-days of admission. These patients were considered as the “Early Mortality” group (death within ≤ 72 hours). Predictors were examined separately due to proportionality.



Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Lactate (per mmol/L)	1.71	1.23 – 2.37	0.001*
pH (per 0.1 unit < 7.35)	3.85	1.54 – 9.62	0.004*
AKI (presence)	11.63	1.36 – 99.28	0.025*
Alcohol Excess (> 14 units/week)	7.49	1.37 – 40.85	0.020*
WCC (per $1 \times 10^9/L < 6.0$)	1.14	1.02 – 1.28	0.021*
LRINEC Score (> 6)	5.82	0.69 – 49.03	0.105
Age (per year)	1.05	0.99 – 1.11	0.101

Table 2: Univariate predictors of early (3-day) mortality (selected variables). * Significant ($p < 0.05$).

Early mortality was significantly associated with severe metabolic derangement, including

- Lower pH (7.21 vs 7.32, $p = 0.0033$)
- Higher lactate (5.88 vs 2.36 mmol/L, $p = 0.0019$)
- Lower white cell counts (7.63 vs $16.22 \times 10^9/L$, $p = 0.0035$)

Discussion and Conclusion

In this cohort of 145 patients, the overall 28-day mortality was 13.2%, however nearly two-fifths of all deaths occurred with the first 72 hours of admission.

The early mortality subgroup was characterised by biochemical findings including hyperlactataemia, acidaemia and an attenuated white cell count. Unsupervised clustering identified a high-risk physiological profile that accounted for the majority of deaths in this cohort.

The presence of a “lethal triad” of elevated lactate, acidaemia,

and low/normal WCC coupled with a high-risk frail phenotype identifies patients at high risk of imminent deterioration. These findings suggest that early mortality in limb SSTIs is driven by a distinct combination of metabolic collapse and immune dysregulation rather than delayed surgical intervention alone.

In this subgroup, physiological collapse outweighs managing adequate source control from surgical debridement. For these patients, early multidisciplinary and family discussions regarding ceiling of care are important.

Early death in severe soft tissue infections involving the limbs is not fully explained by delayed surgical management.

A presence of the biochemical “lethal triad” of elevated lactate, acidaemia, and low/normal WCC combined with a high-risk phenotype of ageing multi-morbid and renally impaired patients identifies a group where physiological collapse appears to be the dominant factor that drives mortality.

References

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