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Original Article

Epidemiology of erysipelas and necrotising soft tissue infections

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ABSTRACT

INTRODUCTION. Erysipelas is a common disease in the emergency department, whereas necrotising soft tissue infections (NSTIs) are rare but more severe. The study aimed to investigate the prevalence, incidence, population-based incidence rate, one-year mortality and clinical presentation of erysipelas and NSTIs, and the aetiology, treatment and recurrence of erysipelas.

METHODS. This was a population-based cohort study including acute non-trauma patients ≥ 18 years old with erysipelas or NSTIs from the Region of Southern Denmark in the period from 1 January 2016 to 19 March 2018.

RESULTS. Among 223,618 acute non-trauma visits, 2,136 had erysipelas (prevalence 1%), and 20 had NSTIs (prevalence 0.01%), 96.7 and 0.89 per 10,000 visits, respectively. The population-based incidence rates were 72.10 per 100,000 person-years for incident cases of erysipelas and 0.94 for NSTIs. One-year mortality was 15% for erysipelas and 25% for NSTIs. Erysipelas and NSTI patients had similar demographics and vital signs. For erysipelas, the predominant pathogen in blood cultures was *Streptococcus dysgalactiae*, with two-thirds of patients treated with narrow-spectrum penicillin. One-third of the erysipelas patients had a prior hospitalisation for the condition, and 7.7% of incident cases had recurrence within one year. Obesity and liver disease were risk factors for recurrence.

CONCLUSIONS. Erysipelas is a common infection in the emergency department, whereas NSTIs are much rarer but also more severe and, at presentation, not distinctive in clinical parameters, which underlines the importance of clinical judgement.

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Erysipelas is a common skin and soft tissue infection (SSTI) that is becoming increasingly frequent and burdens patients and the healthcare system [1, 2]. Necrotising soft tissue infections (NSTIs) are severe and rare SSTIs and also life-threatening differential diagnoses to erysipelas [1]. NSTIs differ from other SSTIs by hyperacute progression and severe ischaemia-related pain, but initial clinical findings are scant. Therefore, it is important to distinguish between erysipelas, which usually only requires antimicrobial treatment, and NSTIs, which necessitate acute operative interventions.

Although erysipelas is a common infection, only a few studies have examined its occurrence. Most studies are restricted to a single department without emphasis on clinical presentation or recurrence [2-5]. In addition, direct comparisons of erysipelas and NSTIs have been investigated primarily in smaller studies, focusing mainly on differences in laboratory values rather than initial patient evaluation [6, 7].

Recurrence is a common complication of erysipelas, leading to significant economic costs and patient distress [2, 8, 9]. Fragile skin, obesity, prior skin trauma, oedema, previous erysipelas, smoking, history of cancer and homelessness are well-known predisposing factors for erysipelas. Risk factors directly linked to recurrences are less well-defined, as they vary with the site of infection; however, lymphoedema appears to be a prominent risk factor regardless of the location of the infection [9]. Previous studies found that infection with group C and group G beta-haemolytic streptococci (GCS/GGS), which typically are asymptomatic colonizers, may be a risk factor for recurrence due to anal carriage [10, 11]. Considering the financial costs and patient morbidity related to admission, exploring risk factors for recurrence requiring acute hospital care is relevant, given that these episodes may be prevented.

This population-based cohort study of adult acute non-traumatic visits with erysipelas or NSTIs to a hospital in the Region of Southern Denmark (RSD) investigated 1) the prevalence, incidence, population-based incidence rate (IR) and one-year mortality of erysipelas and NSTIs, 2) compared the clinical presentation of the two and 3) examined the aetiology, antibiotic treatment and recurrence of erysipelas adjusted for risk factors.

METHODS

Study design, setting and selection of participants

This population-based cohort study included all acute non-trauma patients 18 years or older with an acute visit to a hospital in RSD and a diagnosis of erysipelas or NSTIs from 1 January 2016 to 19 March 2018. The adult population in the RSD was 968,761 Danish citizens at the beginning of 2017.

The hospitals provided 24-hour care and received patients referred by ambulance or a primary care physician. In Denmark, referral is mandatory, and healthcare is tax-funded with free and equal access.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) [12].

Variables and data sources

We extracted data on discharge diagnoses of erysipelas (International Statistical Classification of Diseases, tenth edition (ICD-10; A46) or NSTIs (ICD-10; M726) from a previous dataset [13]. Patients' demographics, primary symptoms, vital signs at arrival and prescribed antibiotic treatment were retrieved from the patient administrative system; microbiological results from skin swabs and blood cultures from the microbiological department data system; and initial laboratory values from the electronic laboratory system of RSD. Each patient visit was linked to the Civil Registration System for death and emigration data, and to the Danish National Patient Registry for the time of death, admission, discharge date and discharge diagnoses. The Charlson Comorbidity Index (CCI) was calculated from the ten years of discharge diagnoses leading up to the index date. The index date was the first acute visit in the study period.

Incident cases were defined as having no prior history of acute hospital visits for erysipelas or NTSIs ten years before the index date. In an unmatched analysis, patients with recurrence were compared to those without.

Data on discharge diagnoses in the previous ten years from the index date were used to investigate possible risk factors for recurrent acute visits with erysipelas. These risk factors encompassed overweight, alcohol overconsumption, hypertension, diabetes, chronic pulmonary disease, liver disease, cardiovascular disease,

renal disease, polyneuropathy, lymphoedema, venous insufficiency, leg ulcers and suspected sepsis as a proxy for infection severity and potential underlying risk factors, e.g., immunosuppression or frailty.

Statistical analysis

Depending on the distribution, continuous variables were summarised with means and standard deviation or medians and IQR, whereas categorical data were outlined with frequencies and percentages.

The proportion of acute non-trauma adult visits with a given diagnosis (erysipelas and NSTI) was calculated by dividing the number of acute non-trauma visits for the given diagnosis by the total number of acute non-trauma visits.

The population-based IR was calculated by dividing the number of incident cases of acute non-trauma adult patients with the given diagnosis by the adult population in RSD as of 1 January 2017, adjusted for a 2.2-year observation period.

For erysipelas recurrence, incident cases were followed from discharge until a new acute erysipelas visit, emigration (before 1 March 2019), death or the end of the one-year follow-up period, whichever came first. For mortality, cases were followed until emigration (before 1 March 2019), death or the end of the one-year follow-up, whichever occurred first.

NSTI cases were excluded from the analysis of aetiology, antibiotic treatment and recurrence because there were fewer than five unique individuals in most categories. This was done to prevent potential identification and comply with privacy regulations.

A multiple logistic regression model was used to calculate crude odds ratios and adjusted odds ratios (aOR) for risk factors for the recurrence of erysipelas.

Statistical analyses were performed using STATA version 17 (Stata Corp., TX, USA).

Ethics

The study was approved by the Danish Patient Safety Authority (3-3013-2272/1), and the processing of personal data was approved by the RSD (17/24904, amendment 20/24502). All data were stored, secured and managed according to the General Data Protection Regulation (GDPR) [14] and the Danish Data Protection Act [15].

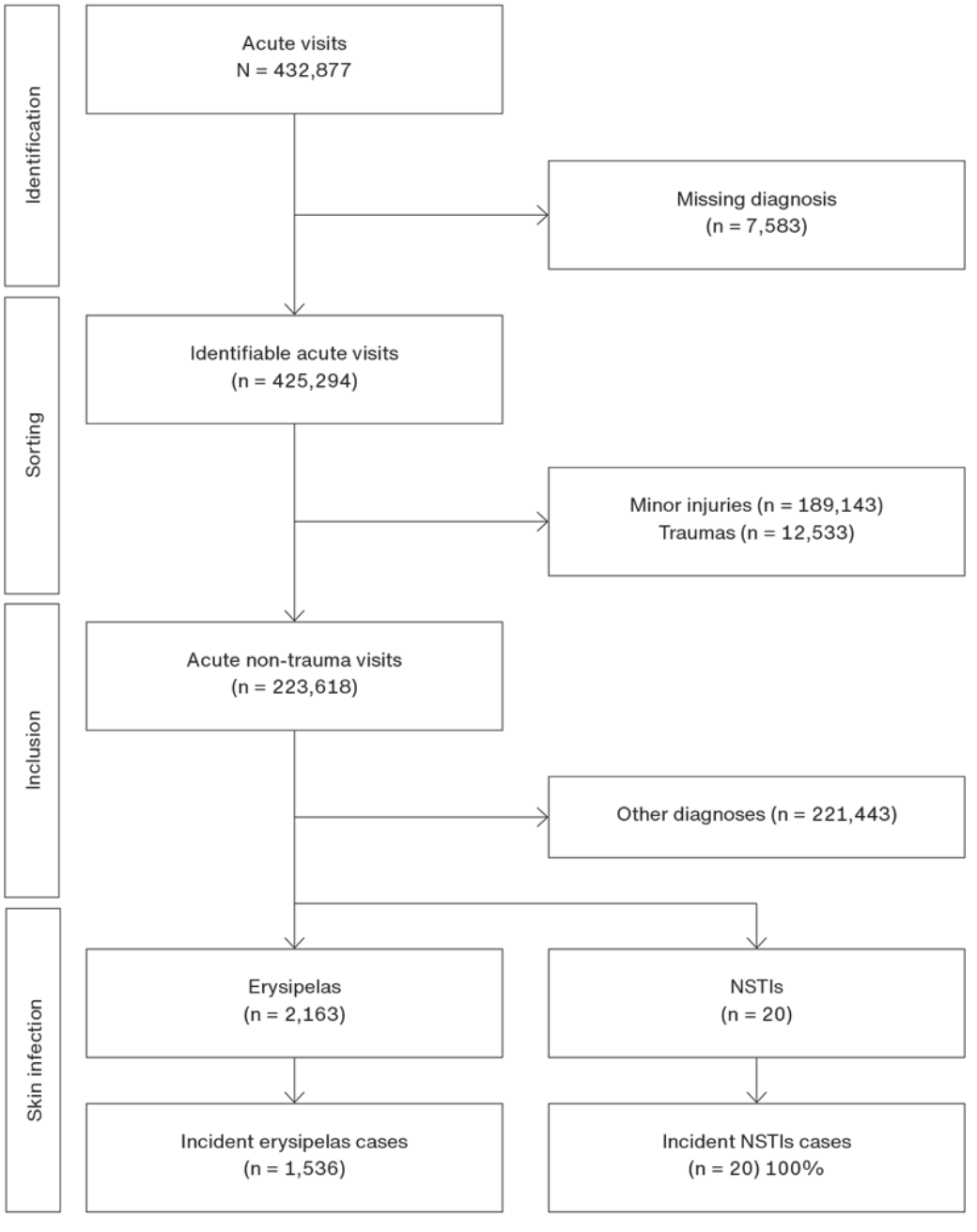
Trial registration: not relevant.

RESULTS

Patients

During the observation period, there were 223,618 acute non-trauma adult visits, of which 2,163 (prevalence of 1.0%) had erysipelas and 20 (prevalence of 0.01%) NSTIs (**Figure 1**). Among the 2,163 visits with erysipelas, 1,536 (71.0%) were incident cases. All NSTIs were incident cases. The proportion of erysipelas visits was 96.7 per 10,000 acute non-trauma visits. The corresponding proportion for NSTIs was 0.89 per 10,000 visits. The adult population-based IR was 72.10 per 100,000 person-years for incident cases of erysipelas and 0.94 per 100,000 for NSTIs.

FIGURE 1 Flow chart identifying and including acute non-trauma adult visits with erysipelas and necrotising soft tissue infections (NSTIs).



Clinical presentation on arrival

Both erysipelas and NSTI patients were predominantly male, with a median age of 69 and 61 years, respectively (**Table 1**). For patients with erysipelas, fever was the most common primary symptom at arrival (50.7%) and was more frequent in patients < 70 years (**Supplementary** Table S1), whereas NSTI patients were more heterogeneous at presentation. One-third of the patients with erysipelas had a prior history of an acute visit with erysipelas.

TABLE 1 Characteristics of the adult acute non-trauma visits with erysipelas or necrotising soft tissue infections.

	Erysipelas	Necrotising soft tissue infections
Total, n (%)	2,163 (99.1)	20 (0.9)
Age, median (IQR), yrs	69 (57-79)	61 (49-70)
Females, n (%)	858 (39.7)	9 (45.0)
Primary symptom on arrival, n (%)		
Fever	1,097 (50.7)	5 (25.0)
Unspecific	689 (31.9)	5 (25.0)
Others	377 (17.4)	10 (50.0)
Charlson Comorbidity Index, n (%)		
0	1,078 (49.8)	10 (50.0)
1	317 (14.7)	3
≥ 2	768 (35.5)	7 (35.0)
Vital signs		
Systolic blood pressure, mean (± SD), mmHg	136 (± 22.6)	131.6 (± 21.0)
Diastolic blood pressure, mean (± SD), mmHg	74.4 (± 16.2)	76 (± 12.7)
Heart rate, mean (± SD), bpm	90.3 (± 19.3)	101.6 (± 17.7)
Respiratory rate, mean (± SD), brpm	19.2 (± 4.8)	20.9 (± 4.5)
Saturation, median (IQR), %	97 (95-98)	97 (96-99)
Glasgow Coma Scale, median (IQR)	15 (15-15)	15 (15-15)
Temperature, mean (± SD), °C	37.8 (± 1.1)	38.5 (± 1.3)
qSOFA ≥ 2, n (%)	59 (2.7)	1 (5.0)
Laboratory values		
White blood cell count, median (IQR), × 10^9/l	12 (9-16)	18 (11-21)
CRP concentration, median (IQR), mg/l	207 (83-353)	271 (219-317)
Length of stay, median (IQR), days	3 (1-7)	26 (19-41)
No previous acute visits with erysipelas within 10 yrs, n (%)	1,536 (71.5)	0
No previous acute visits with necrotising soft tissue infections within 10 yrs, n (%)	0 (0)	0 (0)
1-yr mortality, n (%)	332 (15.3)	5 (25.0)

bpm = beats/min.; brpm = breaths/min.; qSOFA = quick sequential organ failure assessment; SD = standard deviation.

For both diseases, half of the patients had a CCI of 0. Vital signs were normal except for temperature, but very few had organ failure, according to the quick sequential organ failure assessment. White blood cell count and CRP were more elevated in NSTI patients, and they were admitted nearly nine times longer. The one-year mortality was 15.3% for erysipelas and 25.0% for NSTIs.

Aetiology and treatment of erysipelas

For erysipelas, skin swabs were performed in 19% of the cases (**Table 2**). *Staphylococcus aureus* was the most common pathogen, followed by other bacteria and GCS/GGS. Positive blood cultures were found in 7.3% of erysipelas cases, with GCS/GGS as the most common pathogen.

TABLE 2 Bacterial aetiology (skin swabs and blood cultures) and initial in-hospital antibiotic treatment of erysipelas visits (N = 2,163).

Procedure	Type	n (%)
Skin swabs	Group A beta-haemolytic streptococci: *Streptococcus pyogenes*	22 (1.0)
	Group B beta-haemolytic streptococci: *Streptococcus agalactiae*	12 (0.6)
	Group C and G beta-haemolytic streptococci: *Streptococcus dysgalactiae*	57 (2.6)
	Staphylococcus aureus	188 (8.7)
	Others	133 (6.2)
	Negative	235 (10.8)
	Not ordered	1,516 (70.1)
Blood cultures	Group A beta-haemolytic streptococci: *Streptococcus pyogenes*	12 (0.6)
	Group B beta-haemolytic streptococci: *Streptococcus agalactiae*	13 (0.6)
	Group C ang G beta-haemolytic streptococci: *Streptococcus dysgalactiae*	63 (2.9)
	Staphylococcus aureus	16 (0.7)
	Others	55 (2.5)
	Negative	1,473 (68.1)
	Not ordered	531 (24.6)
Initial antibiotic treatment	Benzylpenicillin/phenoxymethylpenicillin	629 (29.1)
	Cloxacillin/dicloxacillin	87 (4.0)
	Combination of benzylpenicillin/phenoxymethylpenicillin and cloxacillin/dicloxacillin	676 (31.3)
	Cefuroxime	208 (9.6)
	Piperacillin-tazobactam	221 (10.2)
	Others[a]	342 (15.8)

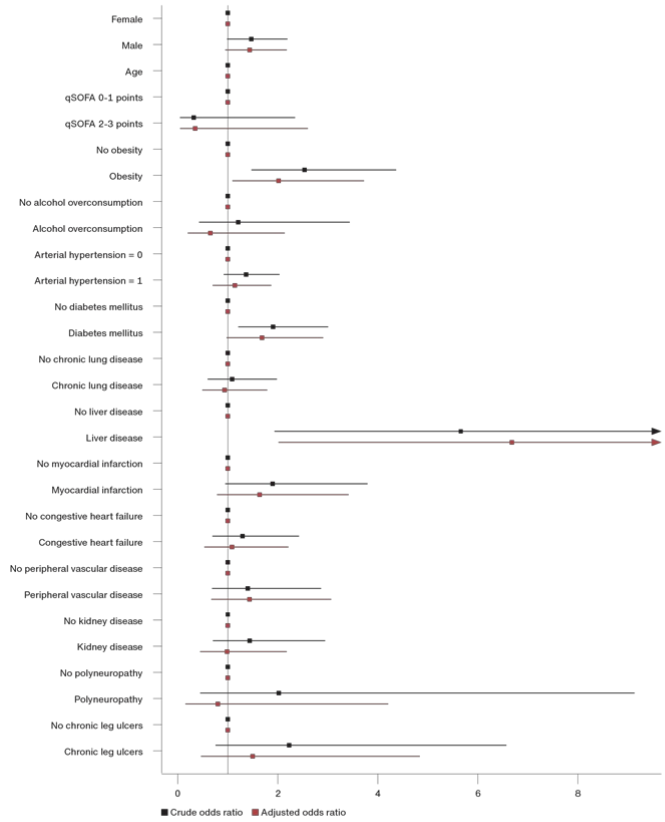
a) Includes carbapenems, macrolides and sulfonamides.

Two-thirds of the patients were treated with benzylpenicillin/phenoxymethylpenicillin alone or combined with cloxacillin/dicloxacillin.

Recurrence of erysipelas

Among the 1,536 erysipelas patients with no prior history of erysipelas (Table 1), 118 (7.7%) had one or more recurrences within the one-year follow-up period (**Figure 2**). After adjusting for possible confounders (listed in Figure 2), we found that obesity (aOR = 2.2) and liver disease (aOR = 6.68) were significant risk factors for acute visits for recurrence of erysipelas within the one-year follow-up period.

FIGURE 2 Forest plot of acute non-trauma visits for incident erysipelas cases[a] with one or more recurrences within one year.



Risk factor	Recurrences of erysipelas, n (%) 0	≥ 1	OR for patients with recurrence (95% CI) crude	adjusted
Overall	1,418 (92.3)	118 (7.7)	NA	NA
Female sex	583 (41.1)	38 (32.2)	1.00 (ref.)	1.00 (ref.)
Male sex	835 (58.9)	80 (67.8)	1.47 (0.98–2.19)	1.44 (0.95–2.18)
Age (median, IQR)	70 (57–81)	66 (56–75)	0.99 (0.98–1.00)	0.99 (0.97–1.00)
qSOFA ≥ 2 on index case	37 (2.6)	< 5[b]	0.32 (0.04–2.35)	0.35 (0.05–2.60)
Obesity	94 (6.6)	18 (15.3)	2.54 (1.47–4.37)	2.02 (1.09–3.72)
Alcohol overconsumption	40 (2.8)	< 5[b]	1.21 (0.42–3.44)	0.65 (0.20–2.14)
Arterial hypertension	387 (27.3)	40 (33.9)	1.37 (0.92–2.04)	1.14 (0.70–1.87)
Diabetes mellitus	191 (13.5)	27 (22.9)	1.91 (1.21–3.01)	1.68 (0.98–2.91)
Chronic pulmonary disease	145 (10.2)	13 (11.0)	1.09 (0.60–1.98)	0.94 (0.49–1.79)
Liver disease	11 (0.8)	5 (4.2)	5.66 (1.93–16.57)	6.68 (2.01–22.17)
Myocardial infarction	66 (4.7)	10 (8.5)	1.90 (0.95–3.79)	1.64 (0.78–3.42)
Congestive heart failure	114 (8.0)	12 (10.2)	1.29 (0.69–2.42)	1.08 (0.53–2.21)
Peripheral vascular disease	79 (5.6)	9 (7.6)	1.40 (0.68–2.87)	1.43 (0.67-3.07)
Kidney disease	77 (5.4)	9 (7.6)	1.44 (0.70–2.95)	0.99-(0.45-2.18)
Polyneuropathy	12 (0.8)	< 5[b]	2.02 (0.45–9.13)	0.80 (0.15-4.21)
Chronic leg ulcers	22 (1.6)	< 5[b]	2.23 (0.75–6.57)	1.50 (0.46-4.84)
Lymphoedema	1,418 (100)	0	NA	NA
Venous insufficiency	1,418 (100)	0	NA	NA

CI = confidence interval; NA = not applicable; OR = odds ratio; qSOFA = quick sequential organ failure assessment.
a) No history of acute visits for erysipelas 10 years before the index date.
b) Cells indicating a count of < 5 unique individuals are denoted as '< 5' to prevent the potential identification of individuals, adhering to privacy and data protection guidelines.

DISCUSSION

In this population-based study with nearly a quarter of a million acute non-trauma visits, we found that erysipelas was 100 times more prevalent and incident than NSTIs. At presentation, both groups' demographics and vital signs were similar. In erysipelas patients, *Staphylococcus aureus* was the most common pathogen detected in skin swabs and *Streptococcus dysgalactiae* in blood cultures. Narrow-spectrum penicillin was the preferred first-line treatment. Recurrent erysipelas was seen in 8% of the patients with no prior history of erysipelas, with obesity and liver disease as substantial risk factors.

Compared to similar studies, ours found a higher incidence and prevalence of erysipelas and NSTIs [2, 16-18]. However, these studies were characterised by much smaller sample sizes, limited to erysipelas cases involving only the legs and had longer inclusion periods for NSTI studies than our study.

Despite a median age of 69 years, one-year mortality was high (15.3%) for erysipelas. Other studies have found a much lower mortality at 1.9% for erysipelas of the legs, although this number increased to 8.1% for patients 85 years and older [2]. This may be due to many patients being treated for erysipelas in primary care in Denmark. A study of NSTIs in England found a one-year mortality of 40%, higher than our 25% – possibly due to fewer comorbidities, different treatment strategies or random variation given our smaller number of cases [17]. In contrast, a Danish study found a one-year mortality of 30%, closely matching our results [18].

Consistent with previous studies of erysipelas, most patients were male, presenting with fever and elevated

inflammatory parameters [10, 11, 16]. Although NSTI patients were less frequently registered with fever and more often presented with nonspecific symptoms, the clinical profile of erysipelas and NSTIs was broadly similar. This overlap underscores the diagnostic challenge of distinguishing these infections upon arrival, highlighting the importance of identifying the few NSTI cases among the more common erysipelas presentations.

Staphylococcus aureus and GCS/GGS were found in most positive skin swabs, and GCS/GGS in blood cultures. Similar findings have been observed in a study of erysipelas aetiology from Sweden [10]. Since a positive culture is usually only available on the following days, these findings may guide clinicians in selecting the initial empirical treatment and not using broad-spectrum antibiotics.

In the incident cases of erysipelas, 7.7% had a recurrent episode leading to a new acute visit during the one-year follow-up. This rate is higher than that reported in a smaller study, likely because we included all acute visits and covered erysipelas at any anatomical site [19].

Our results suggest that obesity and liver disease are risk factors for recurrent acute hospital visits for erysipelas. However, this association may be skewed if patients with liver disease are often admitted primarily for other underlying conditions than erysipelas. We observed no recurrences in patients previously diagnosed with lymphedema or venous insufficiency, contradicting a Swedish study [9]. This discrepancy may potentially originate from different coding practices where these diagnoses are not coded as secondary diagnoses or because these patients seek primary care or are attended to at an outpatient clinic. For future studies, it would be interesting to investigate the incidence of erysipelas in both hospital and primary care settings to get a clearer picture of risk factors specific to recurrence.

Strengths and limitations

First, the study is based on an extensive dataset with over 400,000 acute visits from several hospitals. Second, the dataset provides a comprehensive coupling of parameters, including risk factors, symptoms, vital signs and laboratory and microbiology data, which strengthens the analysis, though risk factors, such as smoking or prior cancer, were unavailable. Third, the attending physician determined the discharge diagnoses, which might introduce misclassification bias, e.g., in septic patients without a focus on the infection. However, a Danish validation study of infection coding found a sensitivity of **70%**, suggesting that coding is sufficiently reliable for broader epidemiological analyses [20]. Fourth, the in-hospital setting might limit the number of patients with recurrence of erysipelas, as we have no data on recurrence cases handled in primary care. Furthermore, patients were only followed for one year. Fifth, our data did not show a difference in clinical presentation between erysipelas and NSTI. However, we did not have information about other clinically relevant factors, e.g., skin manifestations and pain level.

CONCLUSIONS

Erysipelas, a common cause of acute hospital visits, has a high recurrence rate, with obesity and liver disease as significant risk factors. In contrast, NSTIs, though far less frequent, are severe and clinically challenging to distinguish from erysipelas upon hospital arrival due to similar demographics and vital signs. Our study underscores the critical need for sharp diagnostic vigilance to identify the few but severe cases of NSTIs early rather than defaulting to an assumption of erysipelas.

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