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Incidence, comorbidity and mortality in patients with necrotizing soft tissue infections, 2005–2018: A Danish nationwide register-based cohort study

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Abstract

Objective: To assess the incidence, comorbidities, treatment modalities and mortality in patients with necrotizing soft tissue infections (NSTIs) in Denmark.

Design: Nationwide population-based registry study.

Setting: Denmark.

Participants: Danish residents with NSTI between 1 January 2005 and 31 August 2018.

Main outcome measure: Incidence of disease per 100,000 person/year and all-cause mortality at day 90 obtained from Danish National Patient Registry and the Danish Civil Registration System.

Results: 1,527 patients with NSTI were identified, yielding an incidence of 1.99 per 100,000 person/year. All-cause 30-day, 90-day and 1-year mortality were 19.4% (95% CI: 17.4 to 21.5), 25.2% (95% CI: 23.1 to 27.5) and 30.4% (95% CI: 28.0 to 32.8), respectively. Amputation occurred in 7% of the individuals. Diabetes was the most predominant comorbidity affecting 43% of the cohort, while 26% had no comorbidities. Higher age, female sex and increasing comorbidity index were found to be independent risk factors of mortality. Admission to high-volume hospitals was associated with improved survival (OR 0.59, 95% CI 0.45 to 0.77). Thirty-six percent received hyperbaric oxygen therapy (HBOT) as an adjunctive therapy. No change in overall mortality was found over the studied time period.

Conclusion: The present study found that in Denmark, the incidence of NSTI increased; mortality rates remained high and largely unaltered. Diabetes was the most common comorbidity, while higher age, female sex and increasing comorbidity index were associated to increased mortality. Survival was improved in those admitted to hospitals with more expertise in treating NSTI. HBOT was frequently used as an adjunct.

Keywords: Necrotizing Soft Tissue Infection; Incidence; Comorbidity; Survival

Strengths and limitations of this study

- All data linked on an individual level across registries with a substantial high follow-up rate.
- Nationwide cohort resulting in a precise estimate of national incidence, demographics and outcomes in contrast to observational studies.
- Inclusion of more than 1,500 patients with NSTI across a 14-year time period: a relatively large sample size considering the rarity of disease.
- No clinical variables describing the severity of illness were obtainable from the registries, and so there may have been a subsequent lack of important factors that could have been built into the statistical models.

Introduction

Necrotizing soft tissue infection (NSTI) is a severe disease associated with substantial morbidity and mortality. NSTI is characterized by rapidly-progressing soft tissue inflammation and necrosis [1]. The infection can be either mono- or polymicrobial, caused by numerous organisms but most commonly by group A streptococcus [2]. Immediate, aggressive, and radical surgical debridement is key in the management of NSTI. Despite rigorous treatment, patients with NSTI have high mortality rates, risk of amputation, and often have prolonged hospital and rehabilitation stays. Mortality rates can be markedly different (6–41%) [3–7], but a recent, large prospective multicenter study demonstrated a 90-day mortality of 18%, which included the use of adjuvant therapies such as intravenous immunoglobulin (IVIG) and hyperbaric oxygen therapy (HBOT) [2]. Retrospective studies and pathophysiological reasoning have indicated that a delay to the first surgical debridement is associated with increased mortality [10–13]. Surgery should be accompanied by broad-spectrum antibiotics and supportive intensive care, which taken together remain the standard of care in the treatment of NSTI.

HBOT has been advocated as adjunctive therapy to the multidisciplinary course of treatment for NSTI and has in retrospective studies been shown to reduce mortality, particularly in the most critically ill patients [14–16]. As with most other treatment interventions in these patients, no randomized clinical trials investigating the effects of HBOT in these patients have been made [17]. Only 1% of patients with NSTI in the United States received HBOT at specialized centres [16] and although the use of HBOT is not universally accepted as a routine clinical treatment for this disease [18,19], most retrospective clinical studies and larger database studies combined with a large body of preclinical data, may justify its current use as adjuvant therapy to surgery, antibiotic therapy and intensive care support [2-5].

In Denmark, few major teaching hospitals receive patients with NSTI from other hospitals for multidisciplinary care. Of these, one receives patients from all parts of the country for centralized treatment using a multidisciplinary protocol, including HBOT [2]. This should be of benefit, as an increased rate of survival has been shown in patients with NSTI who are treated in high-volume NSTI centers where expertise can be developed [20]. However, as many patients with NSTI have septic shock and multiple organ failure, the delayed time taken for transportation to a centralized treatment hospital by air or road ambulance can pose a risk to life and therefore, is not always feasible.

The epidemiology of NSTI in Denmark has never been fully described, and its nationwide incidence and mortality is unknown. Furthermore, it is not known how many patients are transferred after initial

treatment to a centralized hospital for a multidisciplinary approach, or how many receive HBOT; few centres can offer HBOT to critically ill patients. The aim of this study was to evaluate NSTI incidence and mortality in Denmark with special attention to patients receiving centralized, multidisciplinary treatment, including adjuvant HBOT.

Material and Methods

Setting.

This was a nationwide population-based registry study of patients diagnosed with NSTI between 1 January 2005 and 31 August 2018 in Denmark. Data were obtained from the Danish National Patient Registry (DNPR) [21], the Danish Civil Registration System (CRS) [22] and the Cause of Death Register (CDR) [23]. By law, public hospitals in Denmark are required to prospectively report data to these registries. All data were linked to each separate individual using a unique 10-digit number assigned to every Danish resident living in Denmark and non-Danish citizens patients treated in Denmark.

Data collection.

All NSTI cases in Denmark were identified from the DNPR using International Classification of Diseases-10 (ICD10) codes; M726 (necrotizing fasciitis), M725A (necrotizing fasciitis, before 2012), N498C (Fournier's gangrene) and A480 (gas gangrene). DNPR includes information on hospital contacts, procedures, diagnostic codes, admission, and discharge dates on an individual level. To classify comorbidities, diagnoses were obtained from the DNPR, using the Charlson Comorbidity Index, a well-established classification including more than 17 medical conditions [24]. A weighted Charlson Comorbidity Index was also used, as it has shown good discrimination when predicting in-hospital mortality [25]. We included comorbidity diagnoses from 10 years prior to the NSTI diagnosis.

Data obtained from the CRS included information on sex, date of birth, vital status, date of death or emigration from Denmark. The CDR was used to gain information on cause of death on an individual level. In order to define a 'high-volume NSTI hospital', we identified the lowest number of NSTI patients treated yearly at one of the three major teaching hospitals in Denmark. In assessing procedures related to the NSTI diagnosis, we chose to include only data on surgical interventions, supportive modalities and procedures made within seven days of NSTI diagnosis.

The present study was approved by The Danish Data Protection Agency (P-2019-153) and the Danish Health Data Authority (FSEID-0004419). According to Danish law, the use of observational data from approved

registries does not require ethical approval or informed consent. The study was written in compliance with the Reporting of Studies Conducted using Observational Routinely-collected health Data (RECORD) statement [26] (Supplementary appendix 1). The ICD-10 codes used for extraction of comorbidities are found in the Supplementary appendix 2, and the Health Authorities Classification System (SKS)-codes used for extraction of procedures (surgery and medical procedures/treatments) in Supplementary appendix 3.

For those readers with a special interest, the quality of the DNPR and introduction to the Danish SKS-classification system has been reviewed by Schmidt M et al. [21].

Patient and Public Involvement

No patients were involved in the design, implementation, or dissemination of the results from the present study.

Statistical analysis.

We expressed category characteristics and outcomes as absolute numbers (%) and continuous data was reported as medians (interquartile range [IQR]). Annual incidence was expressed as cases per 100,000 persons per year. Mortality rates were presented as percentages with 95% confidence intervals (CI). Comparisons were performed using Wilcoxon Rank Sum Test for quantitative data and Fisher's exact test for categorical data.

Unadjusted and adjusted multivariable logistic regression models were built to identify risk factors associated with increased mortality. All models included age, sex, and weighted Charlson Comorbidity Index as covariates. Additionally, 'hospital category' and 'number of HBOTs' were included as covariates after showing significant association with survival in univariate analyses. P-values were reported as exact values unless they were <0.001. P-values <0.05 were considered statistically significant. Patients who were lost to follow-up or missing data were excluded from analysis. Statistical analyses were performed with RStudio version 1.0.153 (RStudio, Inc.) and GraphPad Prism version 8.0.2 (GraphPad Inc., La Jolla, Ca, USA).

Results

A total of 1,527 patients with NSTI were identified between 1 of January 2005 and 31 of August 2018, yielding a nationwide NSTI incidence of 1.99 per 100,000 person/year (95%CI: 1.79 to 2.19). Over the period of the study, a trend to an increased number of annual NSTI cases (0.06 per 100.000 person/year, 95%CI: 0.02 to 0.10) was noted (fig 1).

Patient median age was 62 (IQR: 50–72), of which 63% were male. Of the 1,527 patients included, 1,303 (85%) were registered with the diagnosis of necrotizing fasciitis, 155 (10%) with Fournier's gangrene and 362 (24%) with gas gangrene. Two hundred and forty-four (16%) patients were registered with more than one of the diagnoses. A total of 260 (17%) had surgery within 4 weeks before the NSTI diagnosis. Characteristics including comorbidities, hospital category and supportive modalities are presented in Table 1. During the first 90 days after NSTI diagnosis, the median number of days alive and out of hospital were 55 (IQR: 10–76).

Interventions and Supportive Modalities

The majority (1506/1527; 99%) of patients were admitted to an intensive care unit, with 86% being mechanically ventilated and 72% treated with vasopressor/inotrope (Table 2). Two hundred and sixty-eight patients (18%) were treated with renal-replacement therapy (at least one treatment with either hemodialysis or continuous renal-replacement therapy) and 554 (36%) patients were treated with HBOT. These patients received their first HBOT after a median of 4.2 (IQR 2.1-6.2) hours from diagnosis at the admitting hospital. They received a median of three HBOT sessions (IQR 2-3), and 45% received two or more HBOT sessions within 24 hours after arrival. The remaining 974 (64%) patients did not receive HBOT as a treatment modality for their NSTI.

A total of 111 (7%) patients underwent at least one type of amputation within 7 days of NSTI diagnosis. Amputation of the upper leg was the most common, and was seen in 73 (5%) patients, followed by amputation of the lower leg (n=18, 1%), upper arm (n=11, <1%), penis (n=6, <1%), lower arm (n=3, <1%), foot (n=3, <1%) and hand (n=1, <1%). Four patients underwent more than one type of amputation.

Mortality

Six patients were lost to follow-up at Day 90, resulting in a 99.6% follow-up rate. These patients were excluded from the survival analyses. In total, 295 patients died within 30 days of diagnosis (19.4%, 95% CI: 17.4 to 21.5) and 384 within 90 days (25.2%, 95% CI: 23.1 to 27.5) (fig 2). As patients who entered the study in 2018 have not been studied for a full year when the study was ended, these patients were excluded from assessment of 1-year mortality. Of the 1,429 individuals enrolled from 2005 to 2017, 1-year mortality was 30.4% (95% CI: 28.0 to 32.8). Patients who did not survive until Day 30 died after a median of 4 days [IQR: 1-11]. Patients with no previous comorbidities had a 30-day, 90-day and 1-year mortality rate of 11.4%

(95% CI 8.5 to 15.0), 13.7% (95% CI 10.5 to 17.5) and 15.4% (95% CI 11.8 to 19.5), respectively. Mortality rates by comorbidity groups are presented in Table 3.

Multivariable logistic regression models showed that factors associated with an increased 90-day mortality were increasing age, female sex, increased weighted Charlson index and treatment exclusively at low-volume NSTI hospitals (Table 4). Receiving two or more HBOT sessions within 24 hours from diagnosis was not significant in either unadjusted or adjusted analyses. In unadjusted analysis, patients receiving three HBOT sessions had a significantly decreased risk of death (p=0.03) compared to other HBOT-treated patients. However, this was not significant after adjustment for age, sex, and comorbidities (p=0.07). No improved overall survival was found from 2012–2018 compared to 2005–2011 (Table 4).

Three high-volume NSTI hospitals (>8 NSTI cases/annually) were identified. Patients treated at one high-volume NSTI hospital offering HBOT as an adjunct (n=859, including 554 HBOT-treated), had significant decreased risk of death compared to patients treated at one high-volume, non-HBOT hospital (n=125) with Odds Ratios (OR) for 30-day mortality and 90-day mortality of 0.54 (95%CI 0.33 to 0.91, p=0.02) and of 0.61 (95%CI 0.39 to 0.97, p=0.03), respectively. No differences were found in age, sex, or weighted comorbidity index between these high-volume hospitals (p=0.18, p=0.77 and p=0.06, respectively). The 30-day non-survivors died after a median of 4 and 5 days in these two hospital categories.

HBOT-treated NSTI patients had a 30-day mortality of 7.4% (95%CI 5.4 to 9.9) and a 90-day mortality of 13.9 (95%CI 11.1 to 17.1). “Necrotizing fasciitis” (M726/725) was the single most reported cause of death at Day 90 (n=84) followed by “Other fibroblastic disorders” (M728) (n=16) and “Sepsis, unspecified organism” (A419) (n=13).

Discussion

The Danish registries that were used in the present study are unique, in that they can link clinical information to an individual level. Using data drawn from these databases, we studied patients with NSTI in Denmark between 1 January 2005 and 31 August 2018. We found a mean incidence of NSTI of 1.99 per 100,000 inhabitants/year; In a study from Northern Thailand, incidence rates as high as 15.5 per 100,000 inhabitants/year have been observed [27], but the present results are similar to those of New Zealand (1.69 per 100,000 inhabitants/year) [28] and Western Norway (3.0 per 100,000) [29].

During the observation period of approximately 14 years, the incidence of NSTI appeared to increase. Numerous factors may have influenced this finding, including increased awareness of NSTI [30] and changes in the practice of registering diagnoses. However, the trend could represent a true increase in disease incidence, similar to that observed in the United States and New Zealand [28,31]. We found an all-cause 30-day, 90-day and 1-year mortality rate of 19%, 25% and 30%, respectively. In other retrospective studies, mortality varies considerably, with values as high as 41% [7]. The 30-day rate found in the present study is similar to the 28-day mortality rate of 18% reported in a recent French registry study [20] but is substantially higher than an overall mortality of 5–10% reported in a registry study including more than 45,913 NSTI patients [16]. NSTI is rare and no diagnostic criteria exist; in general, the diagnosis is made by the surgeon during surgery. Different classifications are based on location, eponyms, and etiology. The noticeable difference in mortality among studies could reflect the heterogeneity of NSTI patients, but also the complexity of diagnosing NSTI. In our study, 16% of patients had more than one of three codes registered, confirming this complexity. Factors independently associated with higher mortality at Day 90 were older age, female sex, increasing weighted Charlson Index and treatment exclusively at low-volume NSTI hospitals. Increasing age has been reported as a risk factor of death in numerous of studies, but conflicting evidence exists as to whether female sex is an independent risk factor or not [2,20].

Approximately 30% of patients in the present cohort had septic shock; this value is lower than reported recently in a prospective observational study including Scandinavian high-volume hospitals, where 50% had septic shock [2]. Data from the DNPR has shown positive predictive values of 69–82% for septic shock diagnoses, which might explain this difference [32]. However, it is possible that as the hospitals in the Scandinavian study were high-volume and took in a disproportionately large number of severe cases (including septic shock for example), the findings are not directly comparable; the present cohort included all cases, including patients that were not transferred to specialized centres, and thereby represents the overall nationwide incidence. Additional selection bias for severe cases might also be imposed by transport time, as the most severe cases may not be transferred to specialized centres possibly due to transportation constituting a risk in itself. Despite declining mortality rates among patients with sepsis in general [33,34], NSTI still remains a substantial risk of death. In accordance with existing literature [20] we did not find any significant improvement in NSTI survival over the years studied.

Admission to hospitals managing ≥8 NSTI cases annually in this cohort was associated with lower mortality. Admission to hospitals (≥3 NSTI patients per year) was also associated with lower mortality in France [20]. These findings might reflect a greater level of expertise in high-volume hospitals, which are also often able

to offer immediate access to operating theaters and intensive care units with experienced professionals, including microbiologists, infectious disease specialists and dermatologists, at all hours. In deriving our definition of a high-volume NSTI hospital in Denmark, we used a cut-off value that represented the lowest number of NSTI cases treated at one of the three major teaching hospitals in Denmark. These hospitals are the most highly-specialized in the country, with optimal clinical care including a multidisciplinary approach in the treatment of NSTI [18].

Although diabetes may remain a significant burden of disease, it has not been associated with higher mortality rates in NSTI [2]. Diabetes was the most common comorbidity, affecting 43% of patients, followed by 22% with cancer and 19% with chronic pulmonary disease. This varied considerably in comparison to a large French registry study where 29% of patients had diabetes and 9% had cancer [20]. The values from our study are not extraordinarily high, however, the proportion of patients with diabetes affected by NSTI has been reported in previous studies to be as high as 71% [10]. We used the Charlson Comorbidity Index [24] to address burden of diseases, as it is one of the most frequently used comorbidity indexes, especially in survival analysis of cancer [35–37]. However, the index also predicts 30-day and 1-year mortality in intensive care patients, which the results from the present cohort is consistent with [38]. For ease of comparison between studies, we reported the Quan's weighted Charlson comorbidity score, as it is increasingly reported as the only comorbidity variable [25,39].

A 98% positive predictive value has been shown for the Charlson's conditions obtained from the DNPR [40]. Surprisingly, 26% of the patients (n=398) did not have any comorbidities at time of NSTI diagnosis. Validation of the Charlson Comorbidity Index showed an in-hospital mortality of 0.4-2.6% in patients with a comorbidity score of zero. This contrasts with an 11% 30-day mortality among patients with no comorbidities in the present cohort and highlights the severity of the NSTI even for those without pre-existing disease. Recent surgical interventions do pose a risk factor of developing NSTI [1] and nearly one fifth (17%) of the cohort had had surgery within four weeks before NSTI was diagnosed.

An improved 30 and 90-day survival in hospitals offering HBOT as an adjunct to the multidisciplinary treatment was noted. However, these results should be interpreted cautiously due to missing confounders, such as clinical variables and potentially different treatment modalities across hospitals. Mortality among HBOT-treated individuals was noticeably reduced compared to those who did not receive HBOT. This could indicate that HBOT provides a 'real' treatment effect, but the difference is marked and could accentuate a selection bias based upon which patients are offered HBOT as an adjunct. Although access to HBOT is

limited, the early transfer of patients from a primary hospital to a larger, specialized referral centre did not seem to worsen outcome of patients with suspected or confirmed NSTI [20,41,42]. Current recommendations based largely on retrospective clinical studies and preclinical evidence recommend six to seven HBOT sessions within the first 72 hours from admission [43–45]. Our data found that a median number of 3 sessions of HBOT were given in this cohort; this could be looked upon as undertreatment. However, no randomized trials exist that can either recommend or refute the use of HBOT on NSTI patients [17].

Our study has some limitations: first, we did not confirm the NSTI diagnoses retrieved from the DNPR by medical records; second, treatment modalities may vary among hospitals, potentially affecting mortality rates differently; third, in contrast to prospective observational studies, no clinical variables describing the severity of illness (e.g. Simplified Acute Physiology Score (SAPS) III etc.) were obtainable from the registries, and so there may have been a subsequent lack of important factors that could have been built into the statistical models. The strengths of the study were that all patients with a diagnosis of NSTI nationwide were included, resulting in a precise estimate of the national incidence. The diagnoses for Charlson comorbidities, as well as the codes describing the supportive modalities have shown generally high positive predictive values when obtained from the DNPR [21]. Moreover, the present study included data from a large sample size derived over approximately 14 years with a high follow-up rate.

In conclusion, this nationwide study showed that incidence of NSTI is increasing, although mortality rates remain high and largely unaltered. Age, female sex and increasing comorbidities were statically significant independent factors associated with increased mortality. Admission to a high-volume NSTI hospital was associated with lower mortality. In centres treating >8 patients per year, HBOT was associated with decreased odds for mortality.

Contributions: Study planning (MH, MBM, LBM, OH), data analysis (MH, MBM), results interpretation (MH, MBM, LBM, OH), drafting manuscript (MH, OH), revision and approval of final version of manuscript (MH, MBM, LBM, OH). The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Corresponding author serves as guarantor for the present study.

Transparency: The lead author (MH) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Ethical approval: Not required

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Data sharing: Data not available for sharing. For information on how to access to the Danish National Patient Registry, the Danish Civil Registration System and the Cause of Death Register, follow the instructions at https://sundhedsdatastyrelsen.dk/forskerservice

All authors have completed the *Unified Competing Interest form* (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Table 1

Demographics		
Patients (n=1527)		
	Age (years)	62 [50–72]
	Sex, male	966 (63%)
Comorbidities		
	Myocardial infarction	118 (8%)
	Congestive heart failure	227 (15%)
	Peripheral vascular disease	238 (16%)
	Cerebrovascular disease	235 (15%)
	Dementia	53 (4%)
	Chronic pulmonary disease	283 (19%)
	Rheumatologic disease	87 (6%)
	Peptic ulcer disease	116 (8%)
	Mild liver disease	126 (8%)
	Moderate or severe liver disease	63 (4%)
	Diabetes without chronic complications	431 (28%)
	Diabetes with chronic compilations	228 (15%)
	Hemiplegia or paraplegia	40 (3%)
	Renal disease	201 (13%)
	Cancer (any malignancy)	330 (22%)
	Metastatic solid tumor	80 (5%)
	HIV/AIDS	11 (1%)
	Charlson score	1 [0-2]
	Charlson Comorbidity index	
	0	398 (26%)
	1-2	759 (50%)
	3-4	286 (19%)
	≥ 5	84 (6%)
	Weighted Charlson score	2 [0-4]
	Weighted Charlson Comorbidity index	
	0	398 (26%)
	1-2	506 (33%)
	3-4	330 (22%)
	≥ 5	293 (19%)
Hospital category*		
	Low volume (< 8 NSTI/year)	419 (27%)
	High volume (≥ 8 NSTI/year)	1108 (73%)
Period (year)		
	2005–2011	694 (45%)
	2012–2018	833 (55%)
Other		
	Septic shock	472 (31%)
	Surgery <4 weeks prior to diagnosis of NSTI	260 (17%)

Table 1. Data are presented as n (%) or median [IQR]. Comorbidity diagnoses from 10 years prior until NSTI diagnosis. Each comorbidity was defined as by the Charlson conditions (ICD-10 diagnoses in Appendix). Septic shock was defined as the ICD-10 diagnosis "Septic shock" or "Sepsis" and a concurrent diagnosis of inotropes (Diagnoses and supportive modalities in Appendix). IQR, interquartile range; NSTI, necrotizing soft tissue infection. *Defined as the lowest number of NSTI cases annually treated at one of the three main teaching hospitals in Denmark.

Table 2

Interventions	
Surgery	
Amputations	111 (7.7%)
Supportive modalities	
Admission to intensive care unit	1506 (99%)
Mechanical ventilation	1317 (86%)
Use of vasopressor/inotrope	1095 (72%)
Renal-replacement therapy, at least one treatment	268 (18%)
HBOT, at any time	554 (36%)
Hours from diagnosis to first HBOT	4.2 [2.1–6.2]
Number of HBOT	3 [2–3]
≥2 HBOT within 24 hours	252 (45%)

Table 2. Procedures/interventions within 7 days from NSTI diagnosis. Data are presented as n (%) or median [IQR]. IQR, interquartile range; HBOT, Hyperbaric Oxygen Therapy; NSTI, necrotizing soft tissue infection.

Table 3:

All-cause mortality across severity of comorbidity			
Weighted Charlson Index	**30-day mortality**	**90-day mortality**	**1-year mortality***
0	11.4% (95%CI: 8.5-15.0)	13.7% (95%CI: 11.6-18.9)	15.4% (95%CI: 11.8-19.5)
1-2	20.6% (95%CI: 17.1-24.4)	26.3% (95%CI: 22.5-30.4)	31.6% (95%CI: 27.4-36.1)
3-4	25.8% (95%CI: 21.1-30.8)	30.6% (95%CI: 25.7-35.9)	37.3% (95%CI: 31.9-42.9)
≥ 5	20.9% (95%CI: 16.4-26.0)	32.9% (95%CI: 27.5-38.6)	40.4% (95%CI: 34.6-46.4)

*Patients enrolled 2005–2017 (n=1429). CI, Confidence Interval.

Table 4:

Factors associated with 90-day mortality				
Patients (n=1527)	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (years)	1.06 (1.05–1.08)	<0.001	1.06 (1.05–1.07)	<0.001
Sex (male)	0.69 (0.55–0.88)	0.002	0.72 (0.56–0.94)	0.01
Weighted Charlson Comorbidity Index				
0	1 (Ref.)		1 (Ref.)	
1–2	2.27 (1.61–3.24)	<0.001	1.50 (1.03–2.21)	0.04
3–4	2.81 (1.95–4.09)	<0.001	1.64 (1.09–2.48)	0.02
≥ 5	3.10 (2.14–4.55)	<0.001	1.96 (1.31–2.96)	0.001
Hospital category*				
< 8 NSTI/year	1 (Ref.)		1 (Ref.)	
≥ 8 NSTI/year	0.48 (0.38–0.61)	<0.001	0.59 (0.45–0.77)	<0.001
Period (year)				
2005–2011	1 (Ref.)		1 (Ref.)	
2012–2018	1.10 (0.87–1.38)	0.44	0.98 (0.76–1.27)	0.89
HBOT treated individuals (n=554)				
Number of HBOT, total				
1	1 (Ref.)		1 (Ref.)	
2	0.72 (0.37–1.41)	0.34	0.83 (0.38–1.80)	0.64
3	0.49 (0.25–0.94)	0.03	0.49 (0.22–1.05)	0.07
Sessions within 24 hours				
≥ 2 HBOT	1 (Ref.)		1 (Ref.)	
<2 HBOT	1.45 (0.89–2.41)	0.14	1.37 (0.73–2.59)	0.34

Factors associated with 90-day mortality. Adjusted for age, sex and weighted Charlson Comorbidity Index. OR, Odds ratio; CI, Confidence Interval; HBOT, Hyperbaric Oxygen Therapy; NSTI, Necrotizing soft tissue infection. *Defined as the lowest number of NSTI cases annually treated at one of the three main teaching hospitals in Denmark.

Fig 1

Yearly incidences of necrotizing soft tissue infection in Denmark

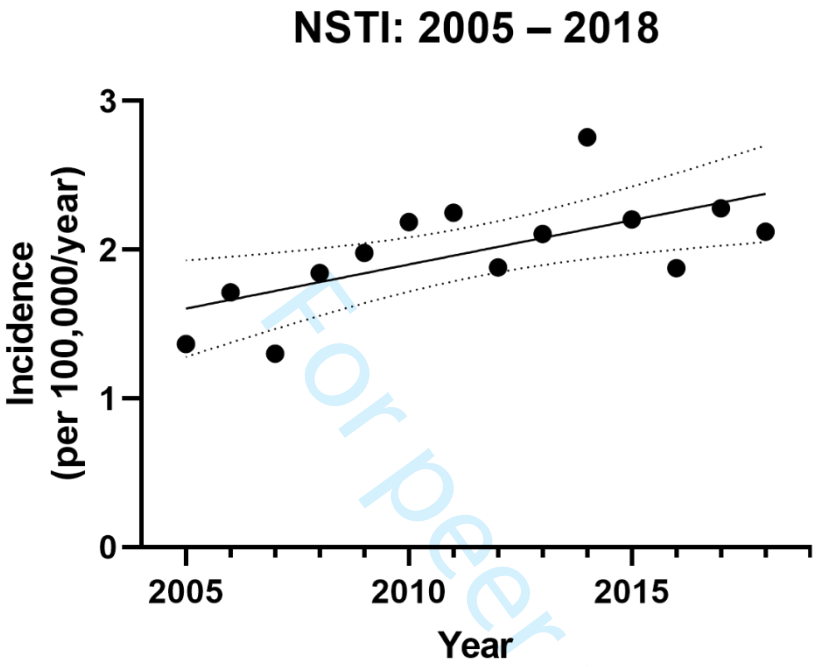

Fig 1. The solid line describes the trend by regression analysis; the dotted lines represent the 95% confidence intervals. NSTI; necrotizing soft tissue infection.

Fig 2 – Survival curve for patients with necrotizing soft tissue infection.

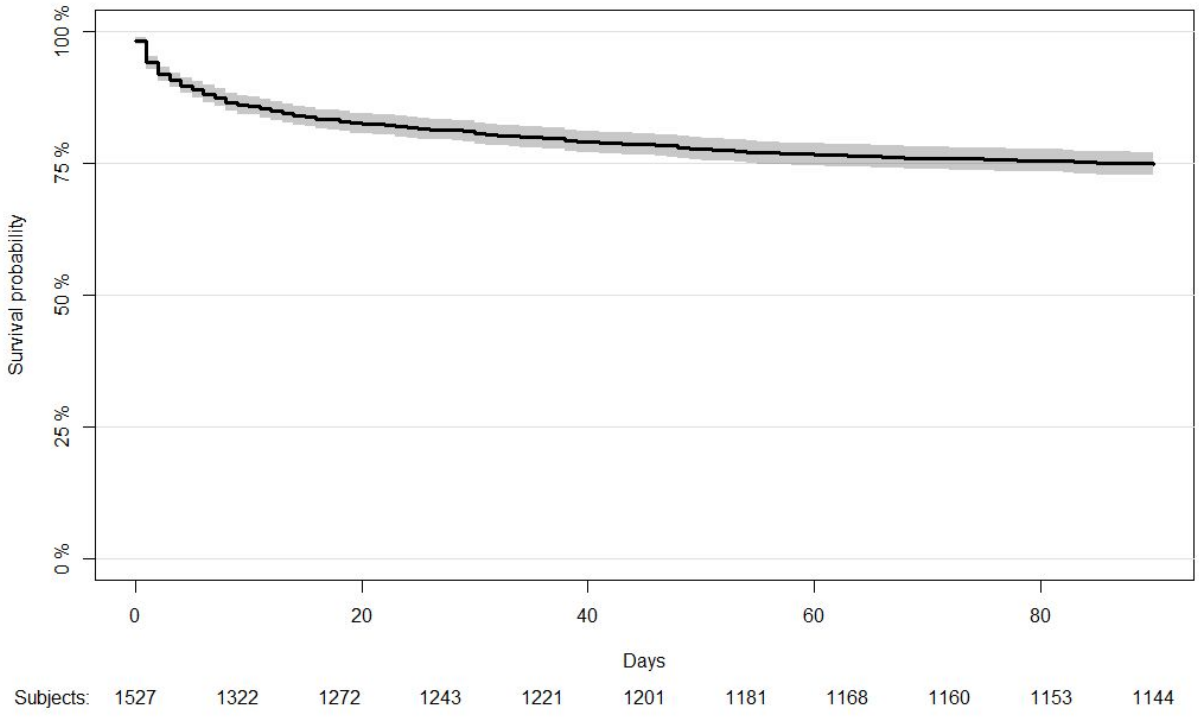

Fig 2. The solid line represents the survival curve. The grey area represents the 95% confidence interval. The survival curve was censored at day 90.

Box 1. BMJ requirement:

What is already known on this topic

- Cohort studies of patients with NSTI have highlighted the severity of disease
- Findings on the association between patient-related risk factors and mortality are inconsistent.
- A description of incidence, comorbidities, treatment modalities and mortality are missing in the nationwide cohort of patients with NSTI.

What this study adds

- Our study shows that the nationwide incidence of NSTI has increased while mortality rates remain high.
- Higher age, female sex and increasing number of comorbidities were independent risk factors for 90-day mortality, while treatment at high-volume hospitals decreased the risk of death.
- In contrast to other countries, hyperbaric oxygen therapy is a frequently used treatment modality for NSTI in Denmark.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title, abstract and material and methods (1st paragraph)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction, paragraph 1-3
Objectives	3	State specific objectives, including any prespecified hypotheses			Introduction paragraph 4
Methods					
Study Design	4	Present key elements of study design early in the paper			Title, abstract, Material and Methods 1st paragraph
Setting	5	Describe the setting, locations, and relevant dates, including			Material and Methods 1st paragraph

		periods of recruitment, exposure, follow-up, and data collection			
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Material and Methods 2nd paragraph (Data collection) includes ICD-10 codes for population selection. Linkage between registries described 1st paragraph of Material and Methods. No flow diagram attached.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	All variables (ICD-10 codes or SKS-codes) listed in Supplemental Appendix A.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).			Material and Methods, paragraph 2+3

		Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias			Material and Methods (last paragraph including statistical analysis). Moreover, potential biases which were not included are addressed in "limitations" section of the discussion.
Study size	10	Explain how the study size was arrived at			-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Material and Methods (statistical analysis)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how			Material and Methods (statistical analysis)

		matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Material and Methods + information on how to retrieve data from DNPR included in "Data Sharing" section.
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Material and Methods 1st paragraph (Person-level)
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Material and Methods (Data Collection).

Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			Results 1st paragraph + Table 1
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			Results section, Table 1+2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Results + subsection "Mortality" including adjusted estimates + Table 4.
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and			-

		interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives			Discussion 1st + 2nd paragraph.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion paragraph 8 "limitations"
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion, entire section.
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion paragraph 8.
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Subsection "Funding Sources"
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Supplemantal information (including ICD-10 + SKS-codes in Supplemental Appendix). How to asceses DNPR

					in “Data Sharing”.

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Appendix 2: ICD-10 codes for Charlson Comorbidity Index

I21	Myocardial infarction
I22	
I252	
I099	Congestive heart failure
I110	
I130	
I132	
I255	
I420	
I425–I429	
I43	
I50	
P290	
I70	Peripheral vascular disease
I71	
I731	
I738	
I739	
I771	
I790	
I792	
K551	
K558	
K559	
Z958	
Z959	
G45	Cerebrovascular disease
G46	
I60–I69	
H340	
F00–F03	Dementia
G30	
F051	
G311	
I278	Chronic pulmonary disease
I279	

J40–J47	
J60–J67	
J684	
J701	
J703	
M05	Rheumatologic disease
M06	
M315	
M32–M34	
M351	
M353	
M360	
K25–K28	Peptic ulcer
G041	Hemiplegia/ paraplegia
G114	
G801	
G802	
G81	
G82	
G830	
G831	
G832	
G833	
G834	
G839	
E100	Diabetes without complications
E101	
E106	
E108	
E109	
E110	
E111	
E116	
E118	
E119	
E120	
E121	

E126	
E128	
E129	
E130	
E131	
E136	
E138	
E139	
E140	
E141	
E146	
E148	
E149	
E102–DE105	Diabetes with chronic complications
E107	
E112	
E115	
E117	
E122–E125	
E127	
E132–E135	
E137	
E142–E145	
E147	
B18	Mild liver disease
K700–K703	
K709	
K713–K715	
K717	
K73	
K74	
K760	
K762–K764	
K768	
K769	
Z944	
I850	Moderate/severe liver disease

I859	
I864	
I982	
K704	
K711	
K721	
K729	
K765–K767	
I120	Renal disease
I131	
N032–N037	
N052–N057	
N18	
N19	
N250	
Z490–Z492	
Z940	
Z992	
C00–C26	Any malignancy (tumor, leukemia, lymphoma)
C30–C34	
C37–C41	
C43	
C45–C58	
C60–C76	
C81–C85	
C88	
C90–C97	
C77–C80	Metastatic solid tumor
B20–B22	HIV/AIDS
B24	

Appendix 3: SKS-codes for different diagnoses

Hyperbaric oxygen therapy:
BGXA6*

Mechanical ventilation:
BGDA0-7

Renal-replacement therapy:
BJFD0, BFJD00, BFJD01, BJFD02

Vasopressor/inotrope:
BFHC93* (excl. BFHC93E-H)
BFHC92*
BFHC95

Intensive care unit admission:
NABB, NABE

Septic shock:
R572
A41.9A (+BFHC92, BFHC93 excl. BFHC93E-H, BFHC95)

Amputations:

Upper arm: KNBQ0, KNBQ01, KNBQ02, KNBQ03, KNBQ99
Lower arm: KNCQ19, KNCQ99, KNDQ1, KNDQ1, KNDQ14, KNDQ16, KNDQ17, KNDQ24, KNDQ26, KNDQ27
Hand: KNDQ99
Pelvis: KNEQ99
Upper leg: KNFQ19, KNFQ29B, KNFQ99
Lower leg: KNGQ19, KNGQ99
Foot: KNHQ1, KNHQ11, KNHQ14, KNHQ17, KNHQ99
Penis: KKGC00-KKGC10

BMJ Open

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Incidence, comorbidity and mortality in patients with necrotizing soft tissue infections, 2005–2018: A Danish nationwide register-based cohort study

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Abstract

Objective: To assess the incidence, comorbidities, treatment modalities and mortality in patients with necrotizing soft tissue infections (NSTIs) in Denmark.

Design: Nationwide population-based registry study.

Setting: Denmark.

Participants: Danish residents with NSTI between 1 January 2005 and 31 August 2018.

Main outcome measure: Incidence of disease per 100,000 person/year and all-cause mortality at day 90 obtained from Danish National Patient Registry and the Danish Civil Registration System.

Results: 1,527 patients with NSTI were identified, yielding an incidence of 1.99 per 100,000 person/year. All-cause 30-day, 90-day and 1-year mortality were 19.4% (95% CI: 17.4 to 21.5), 25.2% (95% CI: 23.1 to 27.5) and 30.4% (95% CI: 28.0 to 32.8), respectively. Amputation occurred in 7% of the individuals. Diabetes was the most predominant comorbidity affecting 43% of the cohort, while 26% had no comorbidities. Higher age, female sex and increasing comorbidity index were found to be independent risk factors of mortality. Admission to high-volume hospitals was associated with improved survival (OR 0.59, 95% CI 0.45 to 0.77). Thirty-six percent received hyperbaric oxygen therapy (HBOT) as an adjunctive therapy. No change in overall mortality was found over the studied time period.

Conclusion: The present study found that in Denmark, the incidence of NSTI increased; mortality rates remained high and largely unaltered. Diabetes was the most common comorbidity, while higher age, female sex and increasing comorbidity index were associated to increased mortality. Survival was improved in those admitted to hospitals with more expertise in treating NSTI. In high-volume hospital, HBOT was associated with decreased odds for mortality.

Keywords: Necrotizing Soft Tissue Infection; Incidence; Comorbidity; Survival

Strengths and limitations of this study

- All data linked on an individual level across registries with a substantial high follow-up rate.
- Nationwide cohort resulting in a precise estimate of national incidence, demographics and outcomes in contrast to observational studies.
- Inclusion of more than 1,500 patients with NSTI across a 14-year time period: a relatively large sample size considering the rarity of disease.
- No clinical variables describing the severity of illness were obtainable from the registries, and so there may have been a subsequent lack of important factors that could have been built into the statistical models.

Introduction

Necrotizing soft tissue infection (NSTI) is a severe disease associated with substantial morbidity and mortality. NSTI is characterized by rapidly-progressing soft tissue inflammation and necrosis [1]. The infection can be either mono- or polymicrobial, caused by numerous organisms but most commonly by group A streptococcus [2]. Immediate, aggressive, and radical surgical debridement is key in the management of NSTI. Despite rigorous treatment, patients with NSTI have high mortality rates, risk of amputation, and often have prolonged hospital and rehabilitation stays. Mortality rates can be markedly different (6–41%) [3–7], but a recent, large prospective multicenter study demonstrated a 90-day mortality of 18%, which included the use of adjuvant therapies such as intravenous immunoglobulin (IVIG) and hyperbaric oxygen therapy (HBOT) [2]. Retrospective studies and pathophysiological reasoning have indicated that a delay to the first surgical debridement is associated with increased mortality [8–11]. Surgery should be accompanied by broad-spectrum antibiotics and supportive intensive care, which taken together remain the standard of care in the treatment of NSTI.

HBOT has been advocated as adjunctive therapy to the multidisciplinary course of treatment for NSTI and has in retrospective studies been shown to reduce mortality, particularly in the most critically ill patients [12–14]. As with most other treatment interventions in these patients, no randomized clinical trials investigating the effects of HBOT in these patients have been made [15]. Only 1% of patients with NSTI in the United States received HBOT at specialized centres [14] and although the use of HBOT is not universally accepted as a routine clinical treatment for this disease [16,17], most retrospective clinical studies and larger database studies combined with a large body of preclinical data, may justify its current use as adjuvant therapy to surgery, antibiotic therapy and intensive care support [2-5]. In Denmark, three HBOT-centres exits; of which two centres offer HBOT using monochambers but only one ICU-capable multi compartment chamber offers adjunctive routine HBOT treatment for NSTI.

In Denmark, few major teaching hospitals receive patients with NSTI from other hospitals for multidisciplinary care. Of these, one receives patients from all parts of the country for centralized treatment using a multidisciplinary protocol, including HBOT [2]. This should be of benefit, as an increased rate of survival has been shown in patients with NSTI who are treated in high-volume NSTI centers where expertise can be developed [18]. However, as many patients with NSTI have septic shock and multiple organ failure, the delayed time taken for transportation to a centralized treatment hospital by air or road ambulance can pose a risk to life and therefore, is not always feasible.

The epidemiology of NSTI in Denmark has never been fully described, and its nationwide incidence and mortality is unknown. Furthermore, it is not known how many patients are transferred after initial treatment to a centralized hospital for a multidisciplinary approach, or how many receive HBOT; only one center offers HBOT to critically ill patients on a routine basis. The aim of this study was to evaluate NSTI incidence and mortality in Denmark with special attention to patients receiving centralized, multidisciplinary treatment, including adjuvant HBOT.

Material and Methods

Setting.

This was a nationwide population-based registry study of patients diagnosed with NSTI between 1 January 2005 and 31 August 2018 in Denmark. Data were obtained from the Danish National Patient Registry (DNPR) [19], the Danish Civil Registration System (CRS) [20] and the Cause of Death Register (CDR) [21]. By law, public hospitals in Denmark are required to prospectively report data to these registries. All data were linked to each separate individual using a unique 10-digit number assigned to every Danish resident living in Denmark and non-Danish citizens patients treated in Denmark.

Data collection.

All NSTI cases in Denmark were identified from the DNPR using International Classification of Diseases-10 (ICD10) codes; M726 (necrotizing fasciitis), M725A (necrotizing fasciitis, before 2012), N498C (Fournier's gangrene) and A480 (gas gangrene). DNPR includes information on hospital contacts, procedures, diagnostic codes, admission, and discharge dates on an individual level. To classify comorbidities, diagnoses were obtained from the DNPR, using the Charlson Comorbidity Index, a well-established classification including more than 17 medical conditions [22]. A weighted Charlson Comorbidity Index was also used, as it has shown good discrimination when predicting in-hospital mortality [23]. We included comorbidity diagnoses from 10 years prior to the NSTI diagnosis.

Data obtained from the CRS included information on sex, date of birth, vital status, date of death or emigration from Denmark. The CDR was used to gain information on cause of death on an individual level. In order to define a 'high-volume NSTI hospital', we identified the lowest number of NSTI patients treated yearly at one of the three major teaching hospitals in Denmark. In assessing procedures related to the NSTI diagnosis, we chose to include only data on surgical interventions, supportive modalities and procedures made within seven days of NSTI diagnosis.

The present study was approved by The Danish Data Protection Agency (P-2019-153) and the Danish Health Data Authority (FSEID-0004419). According to Danish law, the use of observational data from approved registries does not require ethical approval or informed consent. The study was written in compliance with the Reporting of Studies Conducted using Observational Routinely-collected health Data (RECORD) statement [24] (Supplementary appendix 1). The ICD-10 codes used for extraction of comorbidities are found in the Supplementary appendix 2, and the Health Authorities Classification System (SKS)-codes used for extraction of procedures (surgery and medical procedures/treatments) in Supplementary appendix 3.

For those readers with a special interest, the quality of the DNPR and introduction to the Danish SKS-classification system has been reviewed by Schmidt M et al. [19].

Patient and Public Involvement

No patients were involved in the design, implementation, or dissemination of the results from the present study.

Statistical analysis.

We expressed category characteristics and outcomes as absolute numbers (%) and continuous data was reported as medians (interquartile range [IQR]). Annual incidence was expressed as cases per 100,000 persons per year. Mortality rates were presented as percentages with 95% confidence intervals (CI). Comparisons were performed using Wilcoxon Rank Sum Test for quantitative data and Fisher's exact test for categorical data.

Unadjusted and adjusted multivariable logistic regression models were built to identify risk factors associated with increased mortality. All models included age, sex, and weighted Charlson Comorbidity Index as covariates. Additionally, 'hospital category' and 'number of HBOTs' were included as covariates after showing significant association with survival in univariate analyses. P-values were reported as exact values unless they were <0.001. P-values <0.05 were considered statistically significant. Patients who were lost to follow-up were excluded from the analyses. Statistical analyses were performed with RStudio version 1.0.153 (RStudio, Inc.) and GraphPad Prism version 8.0.2 (GraphPad Inc., La Jolla, Ca, USA).

Results

A total of 1,527 patients with NSTI were identified between 1 of January 2005 and 31 of August 2018, yielding a nationwide NSTI incidence of 1.99 per 100,000 person/year (95%CI: 1.79 to 2.19). Over the

period of the study, a trend to an increased number of annual NSTI cases (0.06 per 100.000 person/year, 95%CI: 0.02 to 0.10) was noted (fig 1).

Patient median age was 62 (IQR: 50–72), of which 63% were male. Of the 1,527 patients included, 1,303 (85%) were registered with the diagnosis of necrotizing fasciitis, 155 (10%) with Fournier's gangrene and 362 (24%) with gas gangrene. Two hundred and forty-four (16%) patients were registered with more than one of the diagnoses. A total of 260 (17%) had surgery within 4 weeks before the NSTI diagnosis. Characteristics including comorbidities, hospital category and supportive modalities are presented in Table 1. During the first 90 days after NSTI diagnosis, the median number of days alive and out of hospital were 55 (IQR: 10–76).

Interventions and Supportive Modalities

The majority (1506/1527; 99%) of patients were admitted to an intensive care unit, with 86% being mechanically ventilated and 72% treated with vasopressor/inotrope (Table 2). Two hundred and sixty-eight patients (18%) were treated with renal-replacement therapy (at least one treatment with either hemodialysis or continuous renal-replacement therapy) and 554 (36%) patients were treated with HBOT. These patients received their first HBOT after a median of 4.2 (IQR 2.1-6.2) hours from diagnosis at the admitting hospital. They received a median of three HBOT sessions (IQR 2-3), and 45% received two or more HBOT sessions within 24 hours after arrival. The remaining 974 (64%) patients did not receive HBOT as a treatment modality for their NSTI. Among those patients who were referred to a HBOT-capable hospital, the annual percentage of HBOT-treated patients varied from 56—82% (lowest 2006, highest 2015).

A total of 111 (7%) patients underwent at least one type of amputation within 7 days of NSTI diagnosis. Amputation of the upper leg was the most common, and was seen in 73 (5%) patients, followed by amputation of the lower leg (n=18, 1%), upper arm (n=11, <1%), penis (n=6, <1%), lower arm (n=3, <1%), foot (n=3, <1%) and hand (n=1, <1%). Four patients underwent more than one type of amputation.

Mortality

Six patients were lost to follow-up at Day 90, resulting in a 99.6% follow-up rate. These patients were excluded from the survival analyses. In total, 295 patients died within 30 days of diagnosis (19.4%, 95% CI: 17.4 to 21.5) and 384 within 90 days (25.2%, 95% CI: 23.1 to 27.5) (fig 2). As patients who entered the study in 2018 have not been studied for a full year when the study was ended, these patients were excluded from

assessment of 1-year mortality. Of the 1,429 individuals enrolled from 2005 to 2017, 1-year mortality was 30.4% (95% CI: 28.0 to 32.8). Patients who did not survive until Day 30 died after a median of 4 days [IQR: 1-11]. Patients with no previous comorbidities had a 30-day, 90-day and 1-year mortality rate of 11.4% (95% CI 8.5 to 15.0), 13.7% (95% CI 10.5 to 17.5) and 15.4% (95% CI 11.8 to 19.5), respectively. Mortality rates by comorbidity groups are presented in Table 3.

Multivariable logistic regression models showed that factors associated with an increased 90-day mortality were increasing age, female sex, increased weighted Charlson index and treatment exclusively at low-volume NSTI hospitals (Table 4). Receiving two or more HBOT sessions within 24 hours from diagnosis was not significant in either unadjusted or adjusted analyses. In unadjusted analysis, patients receiving three HBOT sessions had a significantly decreased risk of death (p=0.03) compared to other HBOT-treated patients. However, this was not significant after adjustment for age, sex, and comorbidities (p=0.07). No improved overall survival was found from 2012–2018 compared to 2005–2011 (Table 4).

Three high-volume NSTI hospitals (>8 NSTI cases/annually) were identified. Patients treated at one high-volume NSTI hospital offering HBOT as an adjunct (n=859, including 554 HBOT-treated), had significant decreased risk of death compared to patients treated at one high-volume, non-HBOT hospital (n=125) with Odds Ratios (OR) for 30-day mortality and 90-day mortality of 0.54 (95%CI 0.33 to 0.91, p=0.02) and of 0.61 (95%CI 0.39 to 0.97, p=0.03), respectively. No differences were found in age, sex, or weighted comorbidity index between these high-volume hospitals (p=0.18, p=0.77 and p=0.06, respectively). The 30-day non-survivors died after a median of 4 and 5 days in these two hospital categories.

HBOT-treated NSTI patients had a 30-day mortality of 7.4% (95%CI 5.4 to 9.9) and a 90-day mortality of 13.9 (95%CI 11.1 to 17.1). “Necrotizing fasciitis” (M726/725) was the single most reported cause of death at Day 90 (n=84) followed by “Other fibroblastic disorders” (M728) (n=16) and “Sepsis, unspecified organism” (A419) (n=13).

Discussion

The Danish registries that were used in the present study are unique, in that they can link clinical information to an individual level. Using data drawn from these databases, we studied patients with NSTI in Denmark between 1 January 2005 and 31 August 2018 (Box 1). We found a mean incidence of NSTI of 1.99 per 100,000 inhabitants/year; In a study from Northern Thailand, incidence rates as high as 15.5 per

100,000 inhabitants/year have been observed [25], but the present results are similar to those of New Zealand (1.69 per 100,000 inhabitants/year) [26] and Western Norway (3.0 per 100,000) [27].

During the observation period of approximately 14 years, the incidence of NSTI appeared to increase. Numerous factors may have influenced this finding, including increased awareness of NSTI [28] and changes in the practice of registering diagnoses. However, the trend could represent a true increase in disease incidence, similar to that observed in the United States and New Zealand [26,29]. We found an all-cause 30-day, 90-day and 1-year mortality rate of 19%, 25% and 30%, respectively. In other retrospective studies, mortality varies considerably, with values as high as 41% [7]. The 30-day rate found in the present study is similar to the 28-day mortality rate of 18% reported in a recent French registry study [18] but is substantially higher than an overall mortality of 5–10% reported in a registry study including more than 45,913 NSTI patients [14]. NSTI is rare and no diagnostic criteria exist; in general, the diagnosis is made by the surgeon during surgery. Computed Tomography has demonstrated a sensitivity of 89% and specificity of 93% in diagnostic accuracy[30] and may as well be required in visualization of portal of entry and extension of infection [31,32]. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) has demonstrated varying performances across clinical studies suggesting that the LRINEC should not be used to rule-out NSTI[33,34,30,35]. Different classifications are based on location, eponyms, and etiology. The noticeable difference in mortality among studies could reflect the heterogeneity of NSTI patients, but also the complexity of diagnosing NSTI. In our study, 16% of patients had more than one of three codes registered, confirming this complexity. Factors independently associated with higher mortality at Day 90 were older age, female sex, increasing weighted Charlson Index and treatment exclusively at low-volume NSTI hospitals. Increasing age has been reported as a risk factor of death in numerous of studies, but conflicting evidence exists as to whether female sex is an independent risk factor or not [2,18].

Approximately 30% of patients in the present cohort had septic shock; this value is lower than reported recently in a prospective observational study including Scandinavian high-volume hospitals, where 50% had septic shock [2]. Data from the DNPR has shown positive predictive values of 69–82% for septic shock diagnoses, which might explain this difference [36]. However, it is possible that as the hospitals in the Scandinavian study were high-volume and took in a disproportionately large number of severe cases (including septic shock for example), the findings are not directly comparable; the present cohort included all cases, including patients that were not transferred to specialized centres, and thereby represents the overall nationwide incidence. Additional selection bias for severe cases might also be imposed by transport time, as the most severe cases may not be transferred to specialized centres possibly due to transportation

constituting a risk in itself. Despite declining mortality rates among patients with sepsis in general [37,38], NSTI still remains a substantial risk of death. In accordance with existing literature [18] we did not find any significant improvement in NSTI survival over the years studied.

Admission to hospitals managing ≥8 NSTI cases annually in this cohort was associated with lower mortality. Admission to hospitals (≥3 NSTI patients per year) was also associated with lower mortality in France [18]. These findings might reflect a greater level of expertise in high-volume hospitals, which are also often able to offer immediate access to operating theaters and intensive care units with experienced professionals, including microbiologists, infectious disease specialists and dermatologists, at all hours. In deriving our definition of a high-volume NSTI hospital in Denmark, we used a cut-off value that represented the lowest number of NSTI cases treated at one of the three major teaching hospitals in Denmark. These hospitals are the most highly-specialized in the country, with optimal clinical care including a multidisciplinary approach in the treatment of NSTI [16].

Although diabetes may remain a significant burden of disease, it has not been associated with higher mortality rates in NSTI [2]. Diabetes was the most common comorbidity, affecting 43% of patients, followed by 22% with cancer and 19% with chronic pulmonary disease. This varied considerably in comparison to a large French registry study where 29% of patients had diabetes and 9% had cancer [18]. The values from our study are not extraordinarily high, however, the proportion of patients with diabetes affected by NSTI has been reported in previous studies to be as high as 71% [8]. We used the Charlson Comorbidity Index [22] to address burden of diseases, as it is one of the most frequently used comorbidity indexes, especially in survival analysis of cancer [39–41]. However, the index also predicts 30-day and 1-year mortality in intensive care patients, which the results from the present cohort is consistent with [42]. For ease of comparison between studies, we reported the Quan's weighted Charlson comorbidity score, as it is increasingly reported as the only comorbidity variable [23,43].

A 98% positive predictive value has been shown for the Charlson's conditions obtained from the DNPR [44]. Surprisingly, 26% of the patients (n=398) did not have any comorbidities at time of NSTI diagnosis. Validation of the Charlson Comorbidity Index showed an in-hospital mortality of 0.4-2.6% in patients with a comorbidity score of zero. This contrasts with an 11% 30-day mortality among patients with no comorbidities in the present cohort and highlights the severity of the NSTI even for those without pre-existing disease. Recent surgical interventions do pose a risk factor of developing NSTI [1] and nearly one fifth (17%) of the cohort had had surgery within four weeks before NSTI was diagnosed.

An improved 30 and 90-day survival in hospitals offering HBOT as an adjunct to the multidisciplinary treatment was noted. However, these results should be interpreted cautiously due to missing confounders, such as clinical variables and potentially different treatment modalities across hospitals. Mortality among HBOT-treated individuals was noticeably reduced compared to those who did not receive HBOT. This could indicate that HBOT provides a 'real' treatment effect, but the difference is marked and could accentuate a selection bias based upon which patients are offered HBOT as an adjunct. Fifty-six to eighty-two percentage of the patients who were admitted to a HBOT capable hospital received HBOT. Presumably, some may have been in such critical hemodynamic condition were in-hospital transportation to HBOT were deemed unachievable, thereby indicating that the HBOT-treated patients represent a selected cohort. Although access to HBOT is limited, the early transfer of patients from a primary hospital to a larger, specialized referral centre did not seem to worsen outcome of patients with suspected or confirmed NSTI [18,45,46]. Current recommendations based largely on retrospective clinical studies and preclinical evidence recommend six to seven HBOT sessions within the first 72 hours from admission [47–49]. Our data found that a median number of 3 sessions of HBOT were given in this cohort; this could be looked upon as undertreatment. However, no randomized trials exist that can either recommend or refute the use of HBOT on NSTI patients [15].

Our study has some limitations: first, we did not confirm the NSTI diagnoses retrieved from the DNPR by medical records; second, treatment modalities may vary among hospitals, potentially affecting mortality rates differently; third, in contrast to prospective observational studies, no clinical variables describing the severity of illness (e.g. Simplified Acute Physiology Score (SAPS) III etc.) were obtainable from the registries, and so there may have been a subsequent lack of important factors that could have been built into the statistical models. The strengths of the study were that all patients with a diagnosis of NSTI nationwide were included, resulting in a precise estimate of the national incidence. The diagnoses for Charlson comorbidities, as well as the codes describing the supportive modalities have shown generally high positive predictive values when obtained from the DNPR [19]. Moreover, the present study included data from a large sample size derived over approximately 14 years with a high follow-up rate.

In conclusion, this nationwide study showed that incidence of NSTI is increasing, although mortality rates remain high and largely unaltered. Age, female sex and increasing comorbidities were statistically significant independent factors associated with increased mortality. Admission to a high-volume NSTI

hospital was associated with lower mortality. In centres treating >8 patients per year, HBOT was associated with decreased odds for mortality.

Contributions: Study planning (MH, MBM, LBM, OH), data analysis (MH, MBM), results interpretation (MH, MBM, LBM, OH), drafting manuscript (MH, OH), revision and approval of final version of manuscript (MH, MBM, LBM, OH). The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Corresponding author serves as guarantor for the present study.

Transparency: The lead author (MH) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Ethical approval: Not required

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Data sharing: Data not available for sharing. For information on how to access to the Danish National Patient Registry, the Danish Civil Registration System and the Cause of Death Register, follow the instructions at https://sundhedsdatastyrelsen.dk/forskerservice

All authors have completed the *Unified Competing Interest form* (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial

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Figure legends

Fig 1. Yearly incidences of necrotizing soft tissue infection in Denmark. The solid line describes the trend by regression analysis; the dotted lines represent the 95% confidence intervals. NSTI; necrotizing soft tissue infection.

Fig 2. Survival curve for patients with necrotizing soft tissue infection. The solid line represents the survival curve. The grey area represents the 95% confidence interval. The survival curve was censored at day 90.

Table 1. Patients' Characteristics

Patients (n=1527)		
	Age (years)	62 [50–72]
	Sex, male	966 (63%)
Comorbidities		
	Myocardial infarction	118 (8%)
	Congestive heart failure	227 (15%)
	Peripheral vascular disease	238 (16%)
	Cerebrovascular disease	235 (15%)
	Dementia	53 (4%)
	Chronic pulmonary disease	283 (19%)
	Rheumatologic disease	87 (6%)
	Peptic ulcer disease	116 (8%)
	Mild liver disease	126 (8%)
	Moderate or severe liver disease	63 (4%)
	Diabetes without chronic complications	431 (28%)
	Diabetes with chronic compilations	228 (15%)
	Hemiplegia or paraplegia	40 (3%)
	Renal disease	201 (13%)
	Cancer (any malignancy)	330 (22%)
	Metastatic solid tumor	80 (5%)
	HIV/AIDS	11 (1%)
	Charlson score	1 [0-2]
	Charlson Comorbidity index	
	0	398 (26%)
	1-2	759 (50%)
	3-4	286 (19%)
	≥ 5	84 (6%)
	Weighted Charlson score	2 [0-4]
	Weighted Charlson Comorbidity index	
	0	398 (26%)
	1-2	506 (33%)
	3-4	330 (22%)
	≥ 5	293 (19%)
Hospital category*		
	Low volume (< 8 NSTI/year)	419 (27%)
	High volume (≥ 8 NSTI/year)	1108 (73%)
Period (year)		
	2005–2011	694 (45%)
	2012–2018	833 (55%)
Other		
	Septic shock	472 (31%)
	Surgery <4 weeks prior to diagnosis of NSTI	260 (17%)

Data are presented as n (%) or median [IQR]. Comorbidity diagnoses from 10 years prior until NSTI diagnosis. Each comorbidity was defined as by the Charlson conditions (ICD-10 diagnoses in Appendix). Septic shock was defined as the ICD-10 diagnosis "Septic shock" or "Sepsis" and a concurrent diagnosis of inotropes (Diagnoses and supportive modalities in Appendix). IQR, interquartile range; NSTI, necrotizing soft tissue infection. *Defined as the lowest number of NSTI cases annually treated at one of the three main teaching hospitals in Denmark.

Table 2. Interventions in patients with NSTI.

Surgery		
	Amputations	111 (7.7%)
	Number of surgical interventions	6 [3—10]
Supportive modalities		
	Admission to intensive care unit	1506 (99%)
	Mechanical ventilation	1317 (86%)
	Use of vasopressor/inotrope	1095 (72%)
	Renal-replacement therapy, at least one treatment	268 (18%)
	HBOT, at any time	554 (36%)
	Hours from diagnosis to first HBOT	4.2 [2.1–6.2]
	Number of HBOT	3 [2–3]
	≥2 HBOT within 24 hours	252 (45%)

Procedures/interventions within 7 days from NSTI diagnosis. Data are presented as n (%) or median [IQR]. IQR, interquartile range; HBOT, Hyperbaric Oxygen Therapy; NSTI, necrotizing soft tissue infection.

Table 3. All-cause mortality across severity of comorbidity.

Weighted Charlson Index	30-day mortality	90-day mortality	1-year mortality*
0	11.4% (95%CI: 8.5-15.0)	13.7% (95%CI: 11.6-18.9)	15.4% (95%CI: 11.8-19.5)
1-2	20.6% (95%CI: 17.1-24.4)	26.3% (95%CI: 22.5-30.4)	31.6% (95%CI: 27.4-36.1)
3-4	25.8% (95%CI: 21.1-30.8)	30.6% (95%CI: 25.7-35.9)	37.3% (95%CI: 31.9-42.9)
≥ 5	20.9% (95%CI: 16.4-26.0)	32.9% (95%CI: 27.5-38.6)	40.4% (95%CI: 34.6-46.4)

*Patients enrolled 2005–2017 (n=1429). CI, Confidence Interval.

Table 4. Factors associated with 90-day mortality.

Patients (n=1521)	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (years)	1.06 (1.05–1.08)	<0.001	1.06 (1.05–1.07)	<0.001
Sex (male)	0.69 (0.55–0.88)	0.002	0.72 (0.56–0.94)	0.01
Weighted Charlson Comorbidity Index				
0	1 (Ref.)		1 (Ref.)	
1–2	2.27 (1.61–3.24)	<0.001	1.50 (1.03–2.21)	0.04
3–4	2.81 (1.95–4.09)	<0.001	1.64 (1.09–2.48)	0.02
≥ 5	3.10 (2.14–4.55)	<0.001	1.96 (1.31–2.96)	0.001
Hospital category*				
< 8 NSTI/year	1 (Ref.)		1 (Ref.)	
≥ 8 NSTI/year	0.48 (0.38–0.61)	<0.001	0.59 (0.45–0.77)	<0.001
Period (year)				
2005–2011	1 (Ref.)		1 (Ref.)	
2012–2018	1.10 (0.87–1.38)	0.44	0.98 (0.76–1.27)	0.89
HBOT treated individuals (n=554)				
Number of HBOT, total				
1	1 (Ref.)		1 (Ref.)	
2	0.72 (0.37–1.41)	0.34	0.83 (0.38–1.80)	0.64
3	0.49 (0.25–0.94)	0.03	0.49 (0.22–1.05)	0.07
Sessions within 24 hours				
≥ 2 HBOT	1 (Ref.)		1 (Ref.)	
<2 HBOT	1.45 (0.89–2.41)	0.14	1.37 (0.73–2.59)	0.34

Multivariable logistic regression model adjusted for age, sex and weighted Charlson Comorbidity Index. Six (n=6) patients were lost to follow-up and were not included in the analyses. OR, Odds ratio; CI, Confidence Interval; HBOT, Hyperbaric Oxygen Therapy; NSTI, Necrotizing soft tissue infection. *Defined as the lowest number of NSTI cases annually treated at one of the three main teaching hospitals in Denmark.

Box 1. What is known and what this study adds.

What is already known on this topic:

- Cohort studies of patients with NSTI have highlighted the severity of disease
- Findings on the association between patient-related risk factors and mortality are inconsistent.
- A description of incidence, comorbidities, treatment modalities and mortality are missing in the nationwide cohort of patients with NSTI.

What this study adds:

- Our study shows that the nationwide incidence of NSTI has increased while mortality rates remain high.
- Higher age, female sex and increasing number of comorbidities were independent risk factors for 90-day mortality, while treatment at high-volume hospitals decreased the risk of death.
- In contrast to other countries, hyperbaric oxygen therapy is a frequently used treatment modality for NSTI in Denmark.

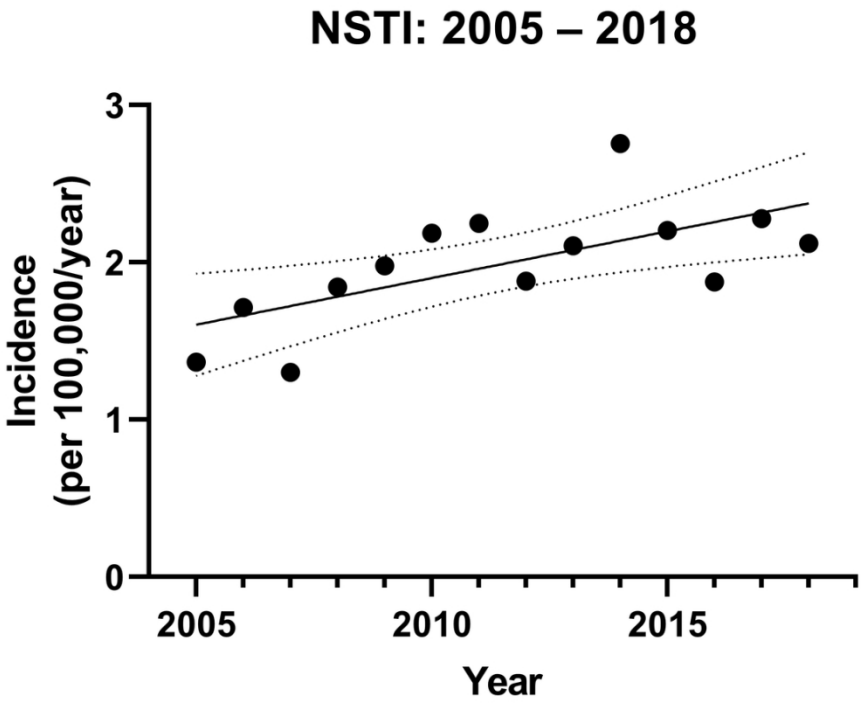

Figure 1. Yearly incidences of necrotizing soft tissue infection in Denmark. The solid line describes the trend by regression analysis; the dotted lines represent the 95% confidence intervals. NSTI; necrotizing soft tissue infection.

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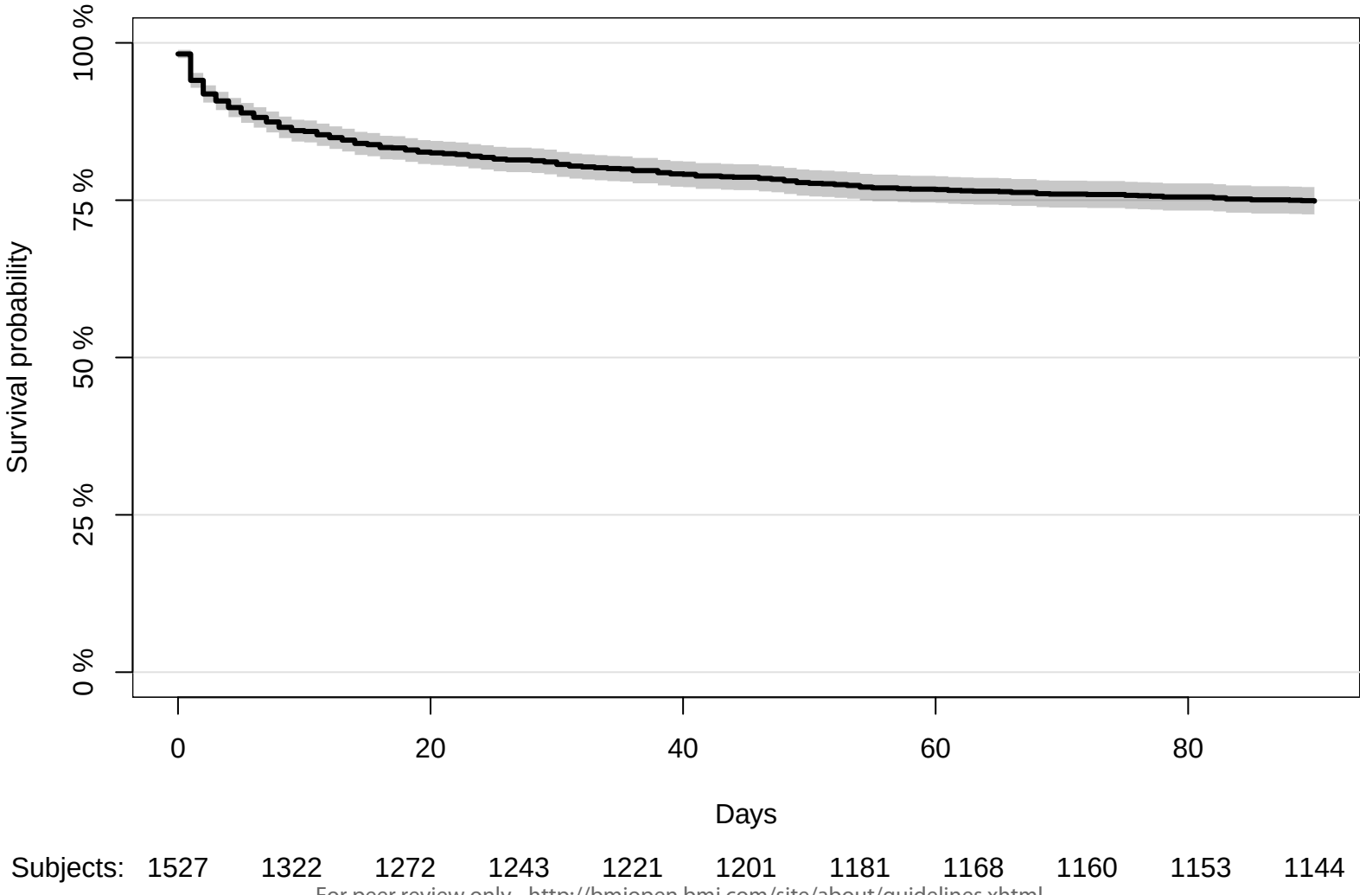

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title, abstract and material and methods (1st paragraph)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction, paragraph 1-3
Objectives	3	State specific objectives, including any prespecified hypotheses			Introduction paragraph 4
Methods					
Study Design	4	Present key elements of study design early in the paper			Title, abstract, Material and Methods 1st paragraph
Setting	5	Describe the setting, locations, and relevant dates, including			Material and Methods 1st paragraph

		periods of recruitment, exposure, follow-up, and data collection			
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Material and Methods 2nd paragraph (Data collection) includes ICD-10 codes for population selection. Linkage between registries described 1st paragraph of Material and Methods. No flow diagram attached.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	All variables (ICD-10 codes or SKS-codes) listed in Supplemental Appendix A.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).			Material and Methods, paragraph 2+3

		Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias			Material and Methods (last paragraph including statistical analysis). Moreover, potential biases which were not included are addressed in "limitations" section of the discussion.
Study size	10	Explain how the study size was arrived at			-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Material and Methods (statistical analysis)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how			Material and Methods (statistical analysis)

		matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Material and Methods + information on how to retrieve data from DNPR included in "Data Sharing" section.
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Material and Methods 1st paragraph (Person-level)
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Material and Methods (Data Collection).

Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			Results 1st paragraph + Table 1
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			Results section, Table 1+2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Results + subsection "Mortality" including adjusted estimates + Table 4.
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and			-

		interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives			Discussion 1st + 2nd paragraph.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion paragraph 8 "limitations"
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion, entire section.
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion paragraph 8.
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Subsection "Funding Sources"
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Supplemantal information (including ICD-10 + SKS-codes in Supplemental Appendix). How to asceses DNPR

					in “Data Sharing”.

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Appendix 2: ICD-10 codes for Charlson Comorbidity Index

I21	Myocardial infarction
I22	
I252	
I099	Congestive heart failure
I110	
I130	
I132	
I255	
I420	
I425–I429	
I43	
I50	
P290	
I70	Peripheral vascular disease
I71	
I731	
I738	
I739	
I771	
I790	
I792	
K551	
K558	
K559	
Z958	
Z959	
G45	Cerebrovascular disease
G46	
I60–I69	
H340	
F00–F03	Dementia
G30	
F051	
G311	
I278	Chronic pulmonary disease
I279	
J40–J47	
J60–J67	
J684	
J701	
J703	
M05	Rheumatologic disease

M06	
M315	
M32–M34	
M351	
M353	
M360	
K25–K28	Peptic ulcer
G041	Hemiplegia/ paraplegia
G114	
G801	
G802	
G81	
G82	
G830	
G831	
G832	
G833	
G834	
G839	
E100	Diabetes without complications
E101	
E106	
E108	
E109	
E110	
E111	
E116	
E118	
E119	
E120	
E121	
E126	
E128	
E129	
E130	
E131	
E136	
E138	
E139	
E140	
E141	
E146	
E148	

E149	
E102–DE105	Diabetes with chronic complications
E107	
E112	
E115	
E117	
E122–E125	
E127	
E132–E135	
E137	
E142–E145	
E147	
B18	Mild liver disease
K700–K703	
K709	
K713–K715	
K717	
K73	
K74	
K760	
K762–K764	
K768	
K769	
Z944	
I850	Moderate/severe liver disease
I859	
I864	
I982	
K704	
K711	
K721	
K729	
K765–K767	
I120	Renal disease
I131	
N032–N037	
N052–N057	
N18	
N19	
N250	
Z490–Z492	
Z940	
Z992	

C00–C26	Any malignancy (tumor, leukemia, lymphoma)
C30–C34	
C37–C41	
C43	
C45–C58	
C60–C76	
C81–C85	
C88	
C90–C97	
C77–C80	Metastatic solid tumor
B20–B22	HIV/AIDS
B24	

Appendix 3: SKS-codes for different diagnoses

Hyperbaric oxygen therapy:
BGXA6*

Mechanical ventilation:
BGDA0-7

Renal-replacement therapy:
BJFD0, BFJD00, BFJD01, BJFD02

Vasopressor/inotrope:
BFHC93* (excl. BFHC93E-H)
BFHC92*
BFHC95

Intensive care unit admission:
NABB, NABE

Septic shock:
R572
A41.9A (+BFHC92, BFHC93 excl. BFHC93E-H, BFHC95)

Amputations:

Upper arm: KNBQ0, KNBQ01, KNBQ02, KNBQ03, KNBQ99
Lower arm: KNCQ19, KNCQ99, KNDQ1, KNDQ1, KNDQ14, KNDQ16, KNDQ17, KNDQ24, KNDQ26, KNDQ27
Hand: KNDQ99
Pelvis: KNEQ99
Upper leg: KNFQ19, KNFQ29B, KNFQ99
Lower leg: KNGQ19, KNGQ99
Foot: KNHQ1, KNHQ11, KNHQ14, KNHQ17, KNHQ99
Penis: KKGC00-KKGC10

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Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction, paragraph 1-3
Objectives	3	State specific objectives, including any prespecified hypotheses			Introduction paragraph 4
Methods					
Study Design	4	Present key elements of study design early in the paper			Title, abstract, Material and Methods 1st paragraph
Setting	5	Describe the setting, locations, and relevant dates, including			Material and Methods 1st paragraph

		periods of recruitment, exposure, follow-up, and data collection			
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Material and Methods 2nd paragraph (Data collection) includes ICD-10 codes for population selection. Linkage between registries described 1st paragraph of Material and Methods. No flow diagram attached.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	All variables (ICD-10 codes or SKS-codes) listed in Supplemental Appendix A.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).			Material and Methods, paragraph 2+3

		Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias			Material and Methods (last paragraph including statistical analysis). Moreover, potential biases which were not included are addressed in "limitations" section of the discussion.
Study size	10	Explain how the study size was arrived at			-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Material and Methods (statistical analysis)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how			Material and Methods (statistical analysis)

		matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Material and Methods + information on how to retrieve data from DNPR included in "Data Sharing" section.
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Material and Methods 1st paragraph (Person-level)
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Material and Methods (Data Collection).

Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			Results 1st paragraph + Table 1
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			Results section, Table 1+2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Results + subsection "Mortality" including adjusted estimates + Table 4.
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and			-

		interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives			Discussion 1st + 2nd paragraph.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion paragraph 8 "limitations"
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion, entire section.
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion paragraph 8.
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Subsection "Funding Sources"
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Supplemantal information (including ICD-10 + SKS-codes in Supplemental Appendix). How to asceses DNPR

					in “Data Sharing”.

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.