PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence, comorbidity and mortality in patients with necrotizing soft tissue infections, 2005–2018: A Danish nationwide register-based cohort study
AUTHORS	Hedetoft, Morten; Madsen, Martin; Madsen, Lærke; Hyldegaard, Ole

VERSION 1 – REVIEW

REVIEWER	Therese Ovesen Department of Clinical Medicine, Aarhus University Regional Hospital West Jutland
REVIEW RETURNED	29-Jun-2020

GENERAL COMMENTS	Dear authors, Thank you for the opportunity to review this register study. I have the following concerns: 1. Statistics: Patients lost to follow up or missing data was excluded. Six patients were lost to follow up, and their data was excluded, I assume. However, it is unclear if other data was missing - how large a proportion of data was incomplete ? Did the final results depend on the exclusion ? 2. Three different types of NSTI were included - it is well known that several demographic factors vary among these three diagnostic categories, and therefore it is relevant to investigate the significance of the specific diagnoses on the outcomes. 3. It appears unclear if HBOT is only available at one hospital in Denmark ? 4. One high volume hospital has received a total of 859 out of 1527 patients. And this hospital offers HBOT - how comes that only 554 were treated with HBOT ? 5. As transportation time/distance plays a major role for the risk of the patient, it is highly relevant to further explore the data set from the hospital offering HBOT: How many of the 859 patients were referred from primary hospitals, and how many patients belonged to the basic catchment area of this particular hospital ? Were there any differences in HBOT treatment between these groups ? It may be anticipated that the HBOT treatment was initiated later and with fewer numbers of HBOT sessions among patients referred from primary hospitals depending on the transportation time/distance. Furthermore, mortality rates ought to be compared between these particular two groups. 6. It should be emphasized that the most critically ill patients are not referred to the high volume HBOT hospital. Due to this selection, mortality rates are higher in low volume hospitals. 7. The only surgical procedure mentioned is amputation - I assume that all patients had multiple soft tissue revision surgeries ? A procedure that is the most determining factor for survival.

	Therefore, the number of patients undergoing revision surgery should be added to table 2. 8. Mortality rates of NSTI also vary considerably across anatomical localization. You should add the anatomical distribution of at least the 725/6 codes. 9. According to the above mentioned concerns, I suggest that you take geography, anatomy, and revision surgery into account as covariates in your statistics. 10. What is the overall conclusion/recommandation ? That all patients should be referred to the only high volume hospital ? Or, that HBOT, more expertise within specialized intensive care etc. should be available on other hospitals as well ? I guess, that you will be able to answer these essential questions when you have solved/addressed the above listed concerns.

REVIEWER	Dr Pieter Bothma James Paget University Hospital London hyperbaric unit United Kingdom
REVIEW RETURNED	04-Jul-2020

GENERAL COMMENTS	On page 12, line 38 it is unclear what is meant with 'statically significant' is it 'statistically'? The difficulty in making the diagnosis makes comparative data difficult to interpret. The authors may consider mentioning the need for better diagnostic parameters, e.g preoperative MRI and post-operative interpretation of histology samples. Views on the benefit or not of LRINEC scoring may be useful for the reader.

REVIEWER	Annette Erichsen Andersson Institute of Health and care sciences, Univerity of Gothenburg, Gothenburg Sweden
REVIEW RETURNED	29-Jul-2020

GENERAL COMMENTS	This is a well written and balanced paper. NSTI is a relative rare and serious disease associated with high morbidity and mortality rates. The interacting mechanisms behind NSTI are not jet fully understood, nor the optimal treatment regimen, thus this paper adds information to the growing knowledge base. Minor correction Reference nr 2: name of journal is lacking.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
1. Statistics: Patients lost to follow up or missing data was excluded. Six patients were lost to follow up, and their data was excluded, I assume. However, it is unclear if other data was missing - how large a proportion of data was incomplete ? Did the final results depend on the exclusion?

ANSWER: We thank the reviewer raising this concern. Except from mortality data on six patients, no data was missing. However, data may have been reported incorrectly, or not at all, to the National Databases, but this is a premise of retrospective register-based studies.

In accordance with the reviewer's concern, we have changed the sentence in the statistical analysis paragraph now stating that data on the six patients who were lost to follow up were excluded from entering mortality analysis (page 5, 2nd last paragraph) and added an additional sentence to the footer of table 4. The issue on predictive values from the present registries are mentioned in the discussion.

2. Three different types of NSTI were included - it is well known that several demographic factors vary among these three diagnostic categories, and therefore it is relevant to investigate the significance of the specific diagnoses on the outcomes.

ANSWER: Thank you for raising this concern. In our study we wanted to include and describe patients with necrotizing soft tissue infections (NSTI). As there is no ICD code for NSTI, we were limited to use alternative codes. This is a limitation of the study. As for all studies on NSTI, the lack of a definition results in less generalizable data, but we think that patients with one or more of these three diagnoses represent patients with NSTI in Denmark. Investing different outcomes between the three diagnoses could be interesting, but it is not the purpose of our study. Furthermore, 16% of the patients in this cohort had two or more of the diagnoses registered, making such an analysis difficult. Ideally, such an analysis should be based on prospectively collected data with access to the patients records if any diagnostic uncertainty arises. Some of the demographic factors may vary between the different subgroups of NSTI. However, these subgroups are not well defined. From our prospective cohort study including 409 patients with NSTI we know, that mortality at day 90 was not related to anatomical localization[1], and in a small prospect study including 55 patients, no differences in age, sex or predisposing factors between Fournier's Gangrene and other NSTIs was seen[2].

3. It appears unclear if HBOT is only available at one hospital in Denmark ?

ANSWER: We agree that this should be stated more clearly. Therefore, a sentence is added to the introduction paragraph stating that three HBOT-centres exist, but only one of these offers ICU-capabilities which is necessary when treating severely ill patients according to EUBS/DHCM statements[3].

4. One high volume hospital has received a total of 859 out of 1527 patients. And this hospital offers HBOT - how comes that only 554 were treated with HBOT ?

ANSWER: From our data we can only speculate on the reasons for not all patients receiving HBOT. First, some of the patients may have been in such a hemodynamical condition, that adjunctive HBOT was not deemed safe. A decision that is determined by the equipment used and internal hospital logistics rather than the effects of HBOT per see. Secondly, some patients may have died before HBOT could be offered. Third, an increased focus on rigorous and precise procedure coding may have taken place. In order to address the reviewers concern, we have now added an additional sentence in the discussion section.

In the present study 64% (554/859) received at least one session of HBOT. The rates of varied from 56% in 2006 to 82% in 2015. We have added this range to the results section.

5. As transportation time/distance plays a major role for the risk of the patient, it is highly relevant to further explore the data set from the hospital offering HBOT: How many of the 859 patients were referred from primary hospitals, and how many patients belonged to the basic catchment area of this particular hospital ? Were there any differences in HBOT treatment between these groups ? It may be anticipated that the HBOT treatment was initiated later and with fewer numbers of HBOT sessions among patients referred from primary hospitals depending on the transportation time/distance.

Furthermore, mortality rates ought to be compared between these particular two groups.

ANSWER: The present high-volume hospital offering HBOT is a highly specialized tertiary hospital with nationwide service treatment for acute and chronic diseases that may require highly specialized therapy. Except from the ENT department where the primary surgical intervention is often performed at the tertiary specialized hospital, no basic catchment area exists to this hospital, and therefore such statistical analyses are—unfortunately—not achievable from the current dataset. Even if the hospital had a general basic catchment area it would not be obtainable from the present registries as this is pseudo-anonymously data and thereby personally identifiable data (including address and catchment area) are not provided.
Interestingly, transportation does not seem to worsen outcome in NSTI[4–8], and the current data do not seem to contradict these findings.

6. It should be emphasized that the most critically ill patients are not referred to the high volume HBOT hospital. Due to this selection, mortality rates are higher in low volume hospitals.

ANSWER: From our data, we can neither confirm nor discard this statement, as we do not have severity scores (e.g. SAPS or SOFA score) on the patients, as these data are not sufficiently reported. We have stated this in the limitations section in the discussion. Also, we are not aware of any studies documenting this. It may be that the most critically ill patients are not referred to high-volume hospitals, as the transportation may pose a greater risk to the patient than not being referred. However, it could be that opposite is true; that the most critically ill patients are referred because they require multidisciplinary intensive therapy which can only be delivered in the high-volume hospital. Lastly, a complicating factor is that in Denmark, distances and thus transportation times are short and the infrastructures as well as helicopter services highly effective.

We have already mentioned an issue of transportation in the introduction.

7. The only surgical procedure mentioned is amputation - I assume that all patients had multiple soft tissue revision surgeries ? A procedure that is the most determining factor for survival. Therefore, the number of patients undergoing revision surgery should be added to table 2.

ANSWER: We agree that the number of surgical revisions would be interesting to report. We have now added the number of surgical interventions to table 2.
Unfortunately, no list of all possible surgical procedures (SKS-codes) covering all types of soft tissue revisions in patients with NSTI exists, and therefore the number of operations represent all types of surgical interventions within 7 days from admission. Yet, the result generated does not seem to be contaminated with non-soft tissue debridements, as we report a median of 6 (3—10) surgical interventions which is comparable to prospectively collected data showing a median number of operations of 4 (3—5) [1].

We therefore believe our revised presentation of the available data is within the given limits and true to quality of the data.

8. Mortality rates of NSTI also vary considerably across anatomical localization. You should add the anatomical distribution of at least the 725/6 codes.

ANSWER: We disagree. In the recently published Scandinavian prospective cohort study previously mentioned, mortality rates did not differ across anatomical localization (head/neck vs. mean; OR 1.34, 95%CI 0.71—2.52, p=0.36. Lower extremity vs. mean; OR 1.26, 95%CI 0.79—2.04, p=0.32. Abdomen/ano-genital area vs. mean; OR 1.42, 95%CI 0.88—2.28, p=0.16)[1]. These findings are in line with another large study (n=109) showing no impact of involvement of the extremities or pelvis[5].

In addition, information on the specific anatomical location is—to our knowledge—not obtainable from the present registries.

9. According to the above mentioned concerns, I suggest that you take geography, anatomy, and revision surgery into account as covariates in your statistics.

ANSWER: Thank you for the suggestion. We choose not to include the suggested variables due to the following: First, as previously described, the high-volume HBOT hospital does not have a basic catchment area. Furthermore, we are not convinced that this is an important variable, and we do not want to increase the number of variables in the survival analysis. Second, mortality does not differ across anatomical localization, as described in the answer to nr. 8, and should therefore not be included in the analyses. Third, we are not convinced that the number of surgical revisions represents severity of NSTI. We do not have data to support this besides from personal experience, but the number of revisions is likely related to the anatomical localization of the infection, as some areas are more difficult to access and to monitor, and thus require repeated revision despite no other signs of disease progression. Also, if included, a revision taking 10 minutes showing healthy tissue would count the same as a 2-hour revision where a lot of tissue is removed.

10. What is the overall conclusion/recommandation ? That all patients should be referred to the only high volume hospital ? Or, that HBOT, more expertise within specialized intensive care etc. should be available on other hospitals as well ? I guess, that you will be able to answer these essential questions when you have solved/addressed the above listed concerns

ANSWER: Thank you for bringing this issue to our attention. As this is a retrospective registry study with its known caveats, we prefer not to make clinical recommendations solely based on the present data but only to report associations between the specified demographic patient data and the specific HBOT interventions when such are found with respect to outcome. In order make the overall conclusions clearer to the reader as requested by the reviewer, the conclusion on our research question which is clearly stated in the last paragraph of the paper is now also clarified in the abstract.

Reviewer 2:
On page 12, line 38 it is unclear what is meant with 'statically significant' is it 'statistically'?

ANSWER: Thanks to the reviewer for pointing out this misspelling. It has now been corrected to statistically.

The difficulty in making the diagnosis makes comparative data difficult to interpret. The authors may consider mentioning the need for better diagnostic parameters, e.g preoperative MRI and post-operative interpretation of histology samples. Views on the benefit or not of LRINEC scoring may be useful for the reader.

ANSWER: NSTI is a surgical diagnosis made by the surgeon from the peri-operatively findings. Therefore, non-invasive procedures such as imaging technologies may potentially add some valuable information in NSTI. Likewise, the LRINEC score seemed robust in the initial published material but has only showed modest PPV/NPV values in the recent years. These concerns have now been shortly described in the discussion section.

Reviewer 3:
This is a well written and balanced paper. NSTI is a relative rare and serious disease associated with high morbidity and mortality rates. The interacting mechanisms behind NSTI are not jet fully understood, nor the optimal treatment regimen, thus this paper adds information to the growing knowledge base.

Minor correction
Reference nr 2: name of journal is lacking.

ANSWER: Thank you; this has now been added to the reference list.

References:
1. Madsen MB, Skrede S, Perner A, et al. Patient' s characteristics and outcomes in necrotising soft - tissue infections : results from a Scandinavian, multicentre, prospective cohort study. Intensive Care Med. 2019;45:1241–1251.
2. Martinschek A, Evers B, Lampl L, et al. Prognostic aspects, survival rate, and predisposing risk factors in patients with Fournier's gangrene and necrotizing soft tissue infections: Evaluation of clinical outcome of 55 patients. Urol Int. 2012;89:173–179.
3. European Underwater and Baromedical Society. Physicians and critical care in hyperbaric chambers. Diving Hyperb Med. 2015;45:42–60.
4. Audureau E, Hua C, de Prost N, et al. Mortality of necrotizing fasciitis: relative influence of individual and hospital-level factors, a nationwide multilevel study, France, 2007–12. Br J Dermatol. 2017;177:1575–1582.
5. Hua C, Sbidian E, Hemery F, et al. Prognostic factors in necrotizing soft-tissue infections (NSTI): A cohort study. J Am Acad Dermatol. 2015;73:1006–12.e8.
6. Brink M, Arnell P, Lycke H, et al. A series of severe necrotising soft-tissue infections in a regional centre in Sweden. Acta Anaesthesiol Scand. 2014;58:882–890.
7. Ingraham AM, Jung HS, Liepert AE, et al. Effect of transfer status on outcomes for necrotizing soft tissue infections. J Surg Res. 2017;220:372–378.
8. Proud D, Bruscino Raiola F, Holden D, et al. Are we getting necrotizing soft tissue infections right? A 10-year review. ANZ J Surg. 2014;84:468–472.

VERSION 2 – REVIEW

REVIEWER	Therese Ovesen Department of Clinical Medicin, Aarhus University ENT department, Regional Hospital West Jutland
REVIEW RETURNED	06-Sep-2020

GENERAL COMMENTS	Thank you for your answers and corrections, which I find appropriate.