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Hyperbaric oxygen treatment in the management of necrotising soft-tissue infections: results from a Danish nationwide registry study

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ABSTRACT

Objectives Application of hyperbaric oxygen (HBO_2) treatment in the multidisciplinary setting of necrotising soft-tissue infection (NSTI) is debated as a considerable number of studies are of low quality with marked prognostication bias due to inadequately addressing disease severity. The objective of this study was to associate HBO_2 treatment with mortality in patients with NSTI including disease severity as a prognostic variable.

Design Nationwide population-based register study.

Setting Denmark.

Participants Danish residents with NSTI patients between January 2011 and June 2016.

Primary and secondary outcome measures Thirty-day mortality was compared between patients receiving and patients not receiving HBO_2 treatment using inverse probability of treatment weighting and propensity-score matching with predetermined variables (age, sex and weighted Charlson comorbidity score, presence of septic shock and Simplified Acute Physiology Score II (SAPS II)).

Results A total of 671 NSTI patients were included with a median age of 63 (52–71), 61% male sex, 30% had septic shock and a median SAPS II of 46 (34–58). Patients who received HBO_2 treatment (n=266) were younger and had lower SAPS II, but a larger fraction had septic shock compared with patients not receiving HBO_2 treatment. Overall, all-cause 30-day mortality was 19% (95% CI 17% to 23%). The statistical models were in general acceptably balanced with covariates reaching <0.1 absolute standardised mean differences and patients receiving HBO_2 treatment were associated with lower 30-day mortality (OR 0.40, 95% CI 0.30 to 0.53, p<0.001).

Conclusions In analyses using inverse probability of treatment weighting and propensity score analysis, patients treated with HBO_2 treatment were associated with improved 30-day survival.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Nationwide cohort with all data linked on an individual level across registries and with a remarkedly high follow-up.
⇒ By applying inverse probability of treatment weighting and propensity-score matching the best qualified estimate on hyperbaric oxygen treatment effect may be achieved which is valuable in planning future trials.
⇒ Simplified Acute Physiology Score II (SAPS II) and presence of septic shock were used as markers of disease severity, but SAPS II was missing in considerable cases.
⇒ Clinical variables (eg, haemodynamical parameters, lactate and vasopressor dosage) may reflect the burden of disease and prognostication more accurately but such variables were not obtainable from the present registries.

BACKGROUND

Necrotising soft-tissue infection (NSTI) is a life-threatening disease. Characterised by its widespread and rapidly progressing necrosis in the soft-tissue compartment,[1] patients with NSTI are critically ill often present with septic shock.[2 3] Surgery, broad-spectrum antibiotics and admission to the intensive care unit are central in the management of NSTI.[1 4]

Regardless of advances in critical care, NSTI mortality rates remain high at approximately 14%–20% by day 30.[2 3 5] Consequently, efforts to lower disease morbidity and mortality are of great importance. Adjuvant hyperbaric oxygen (HBO_2) treatment has been recommended for patients with NSTI,[6 7] but it is not uniformly agreed whether this treatment should be used or not, as no randomised trials have been conducted.[8] HBO_2 treatment involves inhalation of oxygen at pressures above one atmosphere absolute (ATA). Usually, a protocol of 90 min at 2.0–2.8 ATA repeated once or two times a day is used in NSTI management, however, the treatment protocols vary considerably across centres resulting in markedly different cumulative oxygen loads.[9] Likewise, gas gangrene—a subtype of NSTI—is by some hyperbaric centres handled more aggressively due to its particular microbiological properties,[7 10] yet the multidisciplinary handling of these is often equivalent to the rest of NSTI and therefore most commonly included in reporting of

NSTI. The rarity and severity of the condition combined with limited access to properly staffed in-hospital hyperbaric treatment facilities with intensive care equipment results in transportation of patients to hospitals capable of delivering the treatment. Therefore, adjuvant HBO_2 treatment remains highly debated, and in many centres, HBO_2 treatment is not standard of care; in the USA only 1% of the NSTI patients receive HBO_2 treatment.[11] In a recent meta-analysis including observational studies only, HBO_2 treatment was reported to reduce mortality in NSTI, but such data should be cautiously interpreted.[9] Recently, we have documented an immunomodulating effect of HBO_2 treatment in NSTI patients, possibly explaining part of the improved survival.[12–14] Indeed, from a pathophysiological view, these intermittent, short bursts of high-intensity oxygen partial pressure fluctuations induced by HBO_2 have also been shown to have bacteriostatic and bacteriocidic effects by enhancing antibiotic bacterial killing capacity and there is an increasing body of evidence demonstrating the antibacterial effects of oxygen in combination with antibiotics.[15–18]

However, there is a lack of well-conducted clinical studies addressing the suggested beneficial effect of HBO_2 in treatment of NSTI as a considerable number of studies are at critical risk of bias as important confounders such as disease severity are inadequately addressed.[9] Hence, based on data collected from our previous nationwide study[2] this report aimed to determine the association of HBO_2 treatment with survival using propensity score matching including detailed disease severity as a prognostic confounder in patients with NSTI. By applying propensity score matching we achieve two important goals; the closest possible matching of patients either receiving or not receiving HBO_2 treatment the other being a best qualified estimate on HBO_2 treatment effect. Accordingly, we hypothesised that patients receiving HBO_2 treatment as part of their NSTI management had improved survival.

METHODS

Study design and setting

This was a nationwide population-based observational cohort study including patients with an NSTI diagnosis between 1 January 2011 and 30 June 2016 in Denmark. Data were obtained from the Danish National Patient Registry[19] and the Danish Civil Registration System[20] in which public hospitals by law are required to prospectively and routinely report information including data on hospital contacts (admission and discharge dates), diagnoses, surgical and medical procedures/interventions and vital status on an individual level using an unique personal identification number assigned to Danish citizens and residents treated in Denmark. All data are linked on an individual level using the personal identification number. The present time period was chosen as a considerable fraction of missing values on Simplified Acute Physiology Score II (SAPS II) has been reported before 2011[21] and in June 2016, SAPS II was replaced with SAPS 3 in the Danish National Patient Registry. Accordingly, the mode of SAPS II reporting was consistent throughout the reported observation period.

This study is reported in accordance with the Reporting of studies Conducted using Observational Routinely-collected health Data statement[22] and the proposed guidelines for reporting on propensity score analysis[23] and use of multiple imputation.[24]

Participants

Patients with one or more of the following International Classification of Diseases-10 (ICD-10) codes were included; M726 (necrotising fasciitis), M725A (necrotising fasciitis, before 2012), N498C (Fournier's gangrene) and A480 (gas gangrene). No exclusion criteria were used.

Variables

The following variables were extracted from the Danish National Patient Registry; date of NSTI diagnosis, comorbidity diagnoses used in deriving the Charlson Comorbidity Index[25] and an updated weighted Charlson Comorbidity Index,[26] presence of septic shock (defined as ICD-10 diagnosis 'Septic shock' or 'Sepsis' and a concurrent treatment diagnosis of receiving inotropes, SAPS II[27] and treatment with HBO_2 treatment. For a complete list of ICD-10 diagnoses and procedure codes used in generating the above stated conditions and treatment interventions (online supplemental file 1). From the Danish Civil Registration System, we extracted information on sex, age, vital status and date of death/or emigration from Denmark.

Outcomes

The primary outcome measure was the association of HBO_2 treatment with all-cause mortality 30 days after NSTI diagnosis.

Patient and public involvement

No patient involved.

Statistics

Categorical variables are expressed as absolute numbers with percentages (%) and continuous variables as medians with IQRs. Baseline characteristics across groups were compared using Fisher's Exact Test or Wilcoxon rank-sum test as appropriate. As we expected approximately 30% missingness on the SAPS II score[21] and these to be missing at random, we conducted multiple imputations for missing values by chained equations with 25 imputed datasets.[28 29] Patients were divided into two groups according to receiving HBO_2 treatment or not due to their NSTI condition. The association of HBO_2 treatment on 30-day mortality was assessed by using inverse probability of treatment weighting (IPTW) and propensity score analysis in effort of reducing potential confounding in baseline covariates. A logistic regression model was used to estimate the propensity score, whereas a generalised linear model was used to examine 30-day

mortality between groups (link=logit). As recommended, matching variables entering the model were selected on known covariates related to assignment of intervention and to the outcome of interests, consequently we included age, sex and weighted Charlson comorbidity score, presence of septic shock and SAPS II score as covariates.[2 3 30–32] The primary analysis was performed using IPTW. Secondary analyses included nearest neighbour with Mahalanobis distance matching (replacement allowed) and a 1:1 nearest neighbour matching within a calliper of 0.25 (without replacement). Balance in model confounders were assessed by absolute standardised mean differences.[33] We performed a sensitivity analysis on complete cases only to verify the results derived from the multiple imputation model. Moreover, we performed an analysis with patients excluded if dying within 24 hours from diagnosis in effort of testing validity of results as the most severe cases may be represented in this group. Subgroup analyses were performed in patients: (1) with septic shock, (2) without shock, (3) SAPS II above median and (4) SAPS II above upper quartile. We used all available patients from the present registry, and therefore we did not perform a power calculation. P values <0.05 were considered statistically significant. Statistical analyses were performed using Rstudio (Vienna, Austria) with the mice, tidyverse, broom, dplyr, MatchIt and cobalt packages attached.

RESULTS

A total of 671 patients with NSTI were included. No patients were lost to follow-up at day 30. Patients receiving HBO_2 treatment (n=266) were younger and had lower SAPS II than non-HBO_2 treated (n=405) patients, however, a larger fraction of patients who received HBO_2 treatment had septic shock compared with non-HBO_2 patients (table 1). Baseline characteristics among propensity matched groups are presented in online supplemental file 2. Patient receiving HBO_2 treatment received a median of three sessions (IQR 2–3) of HBO_2 treatment (treatment pressure of 284 kPa (18-metre seawater equivalent) of 90 min, no air breaks).

At day 30, 131 patients of the entire cohort had died resulting in an all-cause 30-day mortality of 19% (95% CI 17% to 23%) with 25 (9%) in the HBO_2 treated group and 131 (32%) in the non-HBO_2 treated group. The median day of death was 4 (IQR 1–12). In the propensity models, the propensity score was calculated on age, sex, weighted Charlson comorbidity score, septic shock and SAPS II score. Mortality was significantly decreased in patients receiving HBO_2 treatment compared with non-HBO_2 treated patients (OR 0.40, 95% CI 0.30 to 0.53, table 2) with the included confounders all balanced <0.1 absolute standardised mean differences except for septic shock in IPTW models reaching 0.13 (figure 1).

The SAPS II was not reported in 302 (45%) patients. Differences in age, peripheral vascular disease, moderate/severe liver disease, septic shock and HBO_2 treatment were observed between patients with SAPS II and patients with missing SAPS II (online supplemental file 3). An analysis on the complete case only (n=369) showed comparable results to the primary IPTW-model (OR for death day 30: 0.49, 95% CI 0.32 to 0.74, p<0.001). In a sensitivity analysis excluding the 42 deceased patients within 24 hours from diagnosis, similar results to the primary analysis were observed (OR 0.53, 95% CI 0.38 to 0.73, p<0.001). Subgroup analyses addressing the HBO_2 treatment effect across disease severity are presented in table 3.

DISCUSSION

In this nationwide propensity score-matched cohort study of 671 patients with NSTI, patients receiving HBO_2 treatment were associated with improved 30-day survival.

The beneficial effects of adjunctive HBO_2 treatment in the NSTI management have remained unresolved and debated for decades. Although a number well-conducted observational studies have indicated a reduced mortality rate among patients receiving HBO_2 treatment[34 35] contrasting studies exist reporting no statistical beneficially effect in HBO_2 treated patients with NSTI.[36–40] To date no randomised clinical trials have been performed,[8 9] presumably due to rarity of disease, ethical considerations and disease heterogeneity regarding both anatomical site of infection, disease severity and different interventional approaches applied across centres. However, we strongly encourage researchers within the field to consider performing a properly powered randomised clinical trial leading to validate the present findings and to clarify whether or not HBO_2 should be integrated as a standard in the multidisciplinary management of NSTI. At present, HBO_2 treatment is not recommended in management of NSTI by the Infectious Disease Society of America,[41] whereas the World Society of Emergency Surgery and the Surgical Infection Society Europe considers it to be useful, if available, and not interfering with standard treatment.[42] Likewise, adjunctive HBO_2 treatment for NSTI is endorsed by the European Committee of Hyperbaric Medicine[6] and the Underwater and Hyperbaric Medicine Society.[7]

In the intervening of a randomised trial, propensity score matching analyses may indeed reduce confounding and the resulting biases generated in observational data and provide a useful approximation of the likely effect of treatment.[43 44] The association of HBO_2 treatment on 30-day mortality was unexpectedly high with an OR of 0.40 in favour of HBO_2 treatment, and in subgroup analyses the association seemed more pronounced in the most severe cases (eg, patients with septic shock and patients in SAPS II upper quartile). This could indicate a true beneficial effect, but such results call for cautious interpretation. Selecting the right variables is key in propensity analyses, and incorrectly entered variables may result in bias and could alter the conclusion significantly.[30–32] Variables both related to intervention and outcome of interests seem to result in the least amount of bias.[45] Therefore,

Table 1 Patient's characteristics

	Entire cohort n=671	HBO_2 treated n=266	Non-HBO_2 treated n=405	P value
Age (years)	63 (52–71)	61 (50–68)	65 (53–75)	<0.001
Sex, male	410 (61)	164 (62)	246 (61)	0.87
Comorbidities				
Myocardial infarction	44 (7)	15 (6)	29 (7)	0.52
Congestive heart failure	96 (14)	37 (14)	59 (15)	0.91
Peripheral vascular disease	93 (14)	31 (12)	62 (15)	0.21
Cerebrovascular disease	105 (16)	39 (15)	66 (16)	0.59
Dementia	20 (3)	6 (2)	14 (3)	0.49
Chronic pulmonary disease	119 (18)	41 (15)	78 (19)	0.22
Rheumatological disease	43 (6)	12 (5)	31 (8)	0.11
Peptic ulcer disease	50 (7)	19 (7)	31 (8)	0.88
Mild liver disease	54 (8)	24 (9)	30 (7)	0.47
Moderate/severe liver disease	30 (4)	13 (5)	17 (4)	0.70
Diabetes without chronic complications	186 (28)	81 (30)	105 (26)	0.22
Diabetes with chronic compilations	101 (15)	47 (18)	54 (13)	0.15
Hemiplegia or paraplegia	16 (2)	6 (2)	10 (2)	1
Renal disease	87 (13)	29 (11)	58 (14)	0.24
Cancer (any malignancy)	161 (24)	66 (25)	95 (23)	0.71
Metastatic solid tumour	37 (6)	12 (5)	25 (6)	0.39
HIV/AIDS	4 (<1)	1 (<1)	3 (<1)	1
Charlson score	1 (0–2)	1 (0–2)	1 (1–2)	0.19
Weighted Charlson score	2 (0–4)	2 (0–4)	2 (1–4)	0.23
Weighted Charlson Comorbidity index				
0	174 (26)	75 (28)	99 (24)	0.15
1–2	219 (33)	88 (33)	131 (32)	0.87
3–4	150 (22)	52 (20)	98 (24)	0.18
≥5	128 (19)	51 (19)	77 (19)	1
Septic shock	199 (30)	122 (46)	77 (19)	<0.001
SAPS II	46 (34–58)	44 (33–55)	47 (34–62)	0.01

Data are presented as n (%) or median (IQR). Comorbidity diagnoses from 10 years prior until necrotising soft-tissue infection (NSTI) diagnosis. Each comorbidity was defined as by the Charlson conditions (ICD-10 diagnoses in online supplemental file 1). Septic shock was defined as the ICD-10 diagnosis 'Septic shock' or 'Sepsis' and a concurrent diagnosis of inotropes (diagnoses and treatment intervention codes in online supplemental file 1). SAPS II score was missing 302 patients (45%) and is presented after multiple imputation. Comparisons performed by Wilcoxon rank-sum test.
HBO_2, hyperbaric oxygen; SAPS II, Simplified Acute Physiology Score II.

we chose to include presence of septic shock and SAPS II score as illness severity markers and consequently potential confounders of treatment allocation as well as age, sex and weighted Charlson comorbidity score as prognostic variables for the outcome of interests as these previously have shown to be key variables in NSTI.[2 5 46–52] The fact that the most severe cases had a more pronounced effect seems to be corroborated by larger retrospective studies.[11 53] Yet, the present study might be prone to bias due to unknown confounders that have not been implemented in the present analyses.

Standardised mean difference is a useful tool to assess balance in the propensity analyses generated, and while there is no universally applied threshold of acceptance, a value below 0.1 is regularly considered negligible.[44] In this context, all models seemed acceptably balanced with the covariates reaching values below 0.1 except for septic shock in the IPTW-model reaching a standardised mean difference of 0.13. However, it is important to note that imbalance may still exist between groups as only the measured covariates can be assessed and therefore the present result could be biased due to unmeasured

Table 2 30-day mortality in HBO_2 treated and non-HBO_2 necrotising soft-tissue infection patients

Methods		HBO_2 treated n=266	Non-HBO_2 treated n=405	OR (95% CI)	P value
Unadjusted		25/266 (9%)	131/405 (32%)	0.29 (0.18 to 0.50)	<0.001
Propensity score	IPTW	25/266 (9%)	106/405 (26%)	0.40 (0.30 to 0.53)	<0.001
	NN/w replacement	25/266 (9%)	34/154 (22%)	0.36 (0.21 to 0.64)	<0.001
	1:1	23/225 (10%)	47/225 (21%)	0.43 (0.25 to 0.73)	0.002

Data are presented as absolute number deceased within the given sample size with OR including CIs.
1:1 denotes nearest neighbour matching with 1:1 ratio within a calliper of 0.25 (replacement not allowed).
HBO_2, hyperbaric oxygen; IPTW, inverse probability of treatment weighting; NN, nearest neighbour matching with Mehalanobis distance and replacement allowed.

covariates (eg, lactate, vasopressor dosage, mean arterial pressure and other haemodynamic variables not obtainable from the present registry).

We obtained data from the Danish National Patient Registry which provides detailed administrative and clinical data on an individual level. Overall, the Danish National Patient Registry provides data with high quality, but it should be noted that incomplete registration among covariates may leave unmeasured confounding.[19] However, covariates obtained for the present study have generally shown good positive predictive values with septic shock reaching values of 69%–82%[54] and the Charlson comorbidity index reaching 98%.[55] Whereas, age, sex and vital status obtained from the Civil Registration System are virtually complete as every person residing Denmark is registered.[20]

We expected SAPS II to be missing in approximately 30% of the patients,[21] but in the present NSTI cohort we found SAPS II to be missing in 45%. Although the amount of missing SAPS II values were considerable, we performed multiple imputation as recommended.[56] Yet, it has been suggested that results generated on data with >40% missingness on important variables should only be considered as hypothesis generating.[57 58] Therefore, we performed two sensitivity analyses one on complete cases only and one excluding those not surviving 24 hours from diagnosis, and these were found to be largely in agreement with the primary analysis using the imputed data.

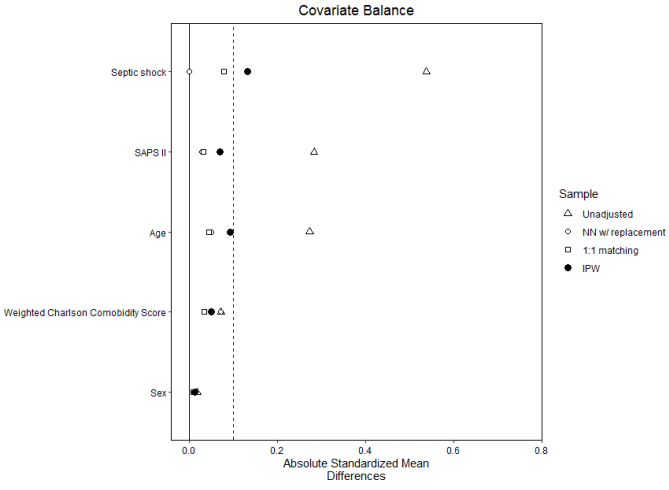

Figure 1 Balance in covariates figured as absolute standardised mean differences according to the unadjusted, nearest neighbour matched (with replacement), 1:1 matching using a within calliper of 0.25 (without replacement) and IPTW models. Dotted line represents the 0.1 threshold. IPW, inverse probability weight; IPTW, inverse probability treatment weighting; NN, nearest neighbour; SAPS II, Simplified Acute Physiology Score II.

HBO_2 treatment is generally considered safe, but is associated with few adverse effects in which most are mild, self-limiting and with no long-term effects. In general, there is a lack of knowledge on side effects observed in critical ill patients such as patients with NSTI who receives HBO_2 treatment presumably due to the rarity of disease and low incidence of observed side effects. Therefore, the majority of side effects have been reported in outpatients and include middle ear barotrauma (4%), oxygen seizures (0.03%) and temporary worsening of short-sightedness.[8]

This study has a series of strengths. We included all patients with NSTI nationwide resulting in an unselected cohort increasing external validity. Considering the rarity of disease, the present sample size is relatively large with a complete follow-up rate. In addition, the general data completeness is high in the present registries, but as stated we found a considerable SAPS II missingness in patients with NSTI.[19 21] We chose all-cause 30-day mortality as the primary outcome as this patient centred outcome is available with a substantial high follow-up in the present registry, and mortality is among the most frequently proposed beneficial effects of HBO_2 in treatment of NSTI.

Several limitations exist. First, the results are limited to association, not causation. Second, although statistical analyses were adjusted for disease severity, the findings may be subject to prognostication bias as the most critically ill patients may have died within a short period time without adequate opportunity to receive HBO_2 treatment. However, the result was unaltered in sensitivity analyses when patients that died within 24 hours from diagnosis were excluded, yet this analysis may not be sufficient to remove the risk of residual confounding completely. Third, only one tertiary hospital provided HBO_2 in treatment of NSTI, and therefore this study may be prone to selection bias as the most haemodynamically instable patients may not have been transferred to this

Table 3 Subgroup analysis of hyperbaric oxygen treatment effects on 30-day mortality according to patients with septic shock, non-shock, SAPS II above median and SAPS II upper quartile

Subgroup	Method	OR (95% CI)	P value
Septic shock	Without adjustment	0.18 (0.08 to 0.36)	<0.001
	Propensity score (IPTW)	0.28 (0.16 to 0.46)	<0.001
Non-shock	Without adjustment	0.31 (0.15 to 0.56)	<0.001
	Propensity score (IPTW)	0.48 (0.33 to 0.69)	<0.001
SAPS II, above median (>46)	Without adjustment	0.40 (0.23 to 0.67)	<0.001
	Propensity score (IPTW)	0.48 (0.34 to 0.67)	<0.001
SAPS II, above upper quartile (>58)	Without adjustment	0.28 (0.13 to 0.58)	<0.001
	Propensity score (IPTW)	0.32 (0.20 to 0.52)	<0.001

Comparisons by univariate (without adjustment) and IPTW analysis.
IPTW, inverse probability of treatment weighting; SAPS II, Simplified Acute Physiology Score II.

hospital as transportation theoretically may constitute a risk in itself, although this statement has been questioned in several studies.[5 48 59] Although, the tertiary hospital has a nationwide service-treatment the patients referred may be selected on unknown factors by the referring physician at the local hospital potentially increasing patient heterogeneity across groups. Fourth, we used SAPS II and presence of septic shock as markers of disease severity in our adjusted analyses, however other clinical variables (eg, haemodynamical parameters, lactate and vasopressor dosage) may reflect the burden of disease and prognostication more accurately but such variables were not obtainable from the present registries. Fifth, a substantial fraction of missing values were present for the SAPS II score, but was controlled by multiple imputations as recommended.[29 60] Yet, its notable that SAPS II was less registered in the cohort not receiving HBO_2 treatment potentially skewing the results observed. Sixth, SAPS II requires 24 hours of admission before a valid score can be registered, thus the most severe cases may be represented among patients with missing values potentially pulling the multiple imputed SAPS II values towards a lowered SAPS score, but the results were found to be similar to the analysis on complete-cases only. Seventh, the analyses were not adjusted with regards to treatment institution due to a large number of referral hospitals in proportion to the number of patients included. Finally, variables are obtained from registries thus the quality of data is dependent on the data quality of the specific registries.

CONCLUSIONS

In the present IPTW and propensity score analyses, patients receiving HBO_2 treatment were associated with improved 30-day survival and the association seemed more pronounced in the most severe cases. Nonetheless, the nature of the design and considerable SAPS II missingness warrant cautious interpretation of the results.

Contributors MH and OH: study planning. MH and MBM: data acquisition. MH: statistical analyses. MH, MBM and OH: results interpretation. MH, MBM and OH: manuscript drafting. All authors read and approved the final manuscript. Corresponding author serves as guarantor for the present study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Study was approved by The Regional Data Agency (P-2019–153) and the Danish Health Data Authority (FSEID-0004419).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available from The Danish Health Data Authority, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Information on how to access the data can be found at www.sundheds datastyrelsen.dk/forskerservice.

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