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Long-term mortality after *Staphylococcus aureus* spondylodiscitis: A Danish nationwide population-based cohort study

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Summary *Objectives:* To determine the long-term mortality and the causes of death after *Staphylococcus aureus* spondylodiscitis.
Methods: Nationwide, population-based cohort study using national registries of adults diagnosed with non-postoperative *S. aureus* spondylodiscitis from 1994–2009 and alive 1 year after diagnosis ($n = 313$). A comparison cohort from the background population individually matched on sex and age was identified ($n = 1565$). Kaplan–Meier survival curves were constructed and Poisson regression analyses used to estimate mortality rate ratios (MRR) adjusted for comorbidity.
Results: 88 patients (28.1%) and 267 individuals from the population-based comparison cohort (17.1%) died. Un-adjusted MRR for *S. aureus* spondylodiscitis patients was 1.77 (95% CI, 1.39–2.25) and 1.32 (95% CI, 1.02–1.71) after adjustment for comorbidity. We observed increased mortality due to infectious (MRR 8.57; 95% CI, 2.80–26.20), endocrine (MRR 3.57; 95% CI, 1.01–12.66), cardiovascular (MRR 1.59; 95% CI, 1.02–2.49), gastrointestinal (MRR 3.21; 95% CI, 1.17–8.84) and alcohol and drug abuse-related (MRR 10.71; 95% CI, 3.23–35.58) diseases.
Conclusions: Patients diagnosed with *S. aureus* spondylodiscitis have substantially increased long-term mortality, mainly due to comorbidity. To improve survival after *S. aureus* spondylodiscitis these patients should be screened for comorbidity and substance abuse predisposing to the disease.

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Introduction

The case-fatality rates reported in case-series of patients with spondylodiscitis are 3–6%,[1–4] but in cases due to *Staphylococcus aureus* infection the rate has been reported to be substantially higher (16%).[5] The most common aetiology in spondylodiscitis is *S. aureus* accounting for half of non-tuberculous cases.[1] One-year all-cause mortality has been reported to be 11.3% in a large series comprising all non-tuberculous spondylodiscitis cases[3] and 2.8–3.5% in a French register study comprising all aetiologies.[4] However, long-term mortality in patients with spondylodiscitis has to our knowledge not been examined previously.

We performed a nationwide, population-based cohort study to determine whether adults who survive the first year after an episode of *S. aureus* spondylodiscitis have increased mortality compared with a population-based comparison cohort. As 72–90% of patients with *S. aureus* spondylodiscitis are reported to have predisposing factors for the acquisition of spondylodiscitis such as severe comorbidity or drug abuse,[1,2,6] we hypothesised that excess mortality would stem mainly from predisposing factors.

Materials and methods

Study design

This study was conducted as a nationwide, population-based cohort study. The study populations were all patients registered with non-postoperative spondylodiscitis in Denmark in the period 1994–2009 with concurrent *S. aureus* bacteraemia who were alive 1 year after diagnosis of spondylodiscitis and a comparison cohort from the background population individually matched on sex and date of birth.

Setting

As of January 2010 Denmark had an estimated population of 5.5 million.[7] Throughout the study period, tax-financed health care has been provided free of charge to all Danish citizens. In 2010 the incidence of *S. aureus* spondylodiscitis was reported to be 1.2/100,000 citizens in Denmark.[8] The proportion of methicillin resistant *S. aureus* in blood isolates has been low (<2%) since 1980.[8]

Data sources

The unique 10-digit Central Person Registration (CPR) number assigned to all Danish citizens at birth or immigration was used to avoid multiple registrations and to track individuals in the following registries, described in detail in Appendix 1.

From The Danish National Patient Register, we extracted the date of first admission for spondylodiscitis, along with data on in- and outpatient admissions of all study participants.[9,10]

From the Danish Staphylococcal Bacteraemia Registry we extracted date of *S. aureus* bacteraemia.[11]

From the Danish Civil Registration System we identified the population-based comparison cohort and extracted data on sex, date of birth, immigration or emigration, loss to follow-up, and death of all study participants.[12]

From the Danish Register of Causes of Death, we extracted the cause-specific mortality as recorded as the underlying cause of death.[13]

From the Danish Cancer Registry we extracted date and type of cancer diagnoses.[14]

Study populations

Patients with *S. aureus* spondylodiscitis

We included all patients who[1] were notified to the Danish National Patient Register with a diagnosis of spondylodiscitis (*International Classification of Diseases 10th Revision [ICD-10]* codes specified in Appendix 2) for the first time during the period 1 January 1994 until 31 December 2009,[2] had *S. aureus* bacteraemia 1 month before until 2 months after date of admission for spondylodiscitis, hereby defining the bacterial aetiology of the spondylodiscitis case to be *S. aureus*,[3] were ≥16 years of age at *S. aureus* spondylodiscitis diagnosis and[4] were born in Denmark and lived in Denmark at the date of *S. aureus* spondylodiscitis diagnosis. To avoid the effect of short-term mortality on the results the study inclusion date was 1 year after *S. aureus* spondylodiscitis diagnosis (as defined in the Danish National Patient Register). Therefore, patients who died, emigrated or were lost to follow-up within the first year after *S. aureus* spondylodiscitis diagnosis were not included in the study. Patients were excluded if the *S. aureus* spondylodiscitis was considered postoperative, defined as any spinal surgical procedure (specified in Appendix 3) performed until 7 days before *S. aureus* spondylodiscitis diagnosis.

Population-based comparison cohort

Individuals in the population-based comparison cohort were individually matched. From the Danish Civil Registration System, we identified for each *S. aureus* spondylodiscitis patient all Danish citizens who were born in Denmark on the same date and were the same sex as the patient and were alive, resident in Denmark and not diagnosed as having spondylodiscitis on the date of study inclusion (i.e. 1 year after diagnosis) of the corresponding *S. aureus* spondylodiscitis patient. From this population, we randomly sampled 5 individuals for the population-based comparison cohort for each patient in the study cohort. Hence, the date of study inclusion for the individuals in the population-based comparison cohort was the same as for the *S. aureus* spondylodiscitis patient to whom they were matched.

Comorbidity

The Charlson Comorbidity Index (CCI) is derived from 12 indicator disease categories and assigns a score of 0–6 to an individual as an indicator of comorbidity burden and is a strong predictor of mortality.[15,16] The diagnoses used from the Danish National Patient Register to assess CCI score has been validated recently by Thygesen et al.[17]