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ORIGINAL ARTICLE

Comorbidity and risk of infection among patients with hip fracture: a Danish population-based cohort study

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Abstract

Summary Impact of comorbidity on infection risk among hip fracture patients is unclear. We found high incidence of infection. Comorbidity was an important risk factor for infection up to 1 year after surgery. Results indicates a need for additional investment in pre- and postoperative programs that assist patients with high comorbidity.

Purpose Comorbidity level and incidence of infection have increased among older patients with hip fracture. The impact of comorbidity on infection risk is unclear. We conducted a cohort study examining the absolute and relative risks of infection in relation to comorbidity level among hip fracture patients.

Methods Utilizing Danish population-based medical registries, we identified 92,600 patients aged ≥ 65 years undergoing hip fracture surgery between 2004 and 2018. Comorbidity was categorized by Charlson comorbidity index scores (CCI): none (CCI = 0), moderate (CCI = 1–2), or severe (CCI ≥ 3). Primary outcome was any hospital-treated infection. Secondary outcomes were hospital-treated pneumonia, urinary tract infection, sepsis, reoperation due to surgical-site infection (SSI), and a composite of any hospital- or community-treated infection. We calculated cumulative incidence and hazard ratios (aHRs) adjusted for age, sex, and surgery year, including 95% confidence intervals (CIs).

Results Prevalence of moderate and severe comorbidity was 40% and 19%, respectively. Incidence of any hospital-treated infection increased with comorbidity level within 0–30 days (none 13% vs. severe 20%) and 0–365 days (none 22% vs. 37% severe). Patients with moderate and severe comorbidity, compared to no comorbidity, had aHRs of 1.3 (CI: 1.3–1.4) and 1.6 (CI: 1.5–1.7) within 0–30 days, and 1.4 (CI: 1.4–1.5) and 1.9 (CI: 1.9–2.0) within 0–365, respectively. Highest incidence was observed for any hospital- or community-treated infection (severe 72%) within 0–365 days. Highest aHR was observed for sepsis within 0–365 days (severe vs. none: 2.7 (CI: 2.4–2.9)).

Conclusion Comorbidity is an important risk factor for infection up to 1 year after hip fracture surgery.

Keywords Cohort · Comorbidity · Epidemiology · Hip fracture · Infections

Introduction

Hip fracture is a major burden worldwide. In 2019, the global incidence of hip fracture was estimated to be more than 14 million, a 93% increase from the estimated incidence in 1990 [1]. Surgery for hip fracture carries a risk of serious complications, with infection being among the most common and serious in older patients [2]. Pneumonia and urinary tract infection (UTI) are the most common postoperative infections [2, 3]. Surgical-site infections (SSIs) that require reoperation are of major clinical relevance due to the severity and complexity of treatment [4]. The 30-day mortality is 2-fold higher in hip fracture patients who develop infection compared to patients without (15% versus 8%) [5], and infections are among the most frequent causes of

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death among patients with hip fracture [6]. From 2005 to 2016, a relative increase in 30-day and 1-year risk of any hospital-treated infection among Danish patients with hip fracture was observed at 30% and 25%, respectively. The use of community-based antibacterial drugs increased as well. Similar trends were not detected in a matched general-population cohort [7].

Comorbidity is becoming more common as the global population ages. The prevalence of hip fracture patients with comorbidities is high and has increased steadily over the last 30 years [8]. However, little attention has been given to comorbidity as a risk factor for infection after hip fracture surgery. The few studies on this topic have various limitations, including small sample size [9, 10], selected study population [9, 10], unknown or short follow-up period [9, 10], or a focus on a specific infection rather than multiple infection types [10, 11]. Notably, clinical guidelines on the treatment of hip fracture do not take comorbidity into account in the surgical decision-making concerning infection risk [12, 13].

To evaluate a need for additional investment in pre- and postoperative programs that assist patients with high comorbidity to improve patient safety, we conducted a population-based cohort study among all Danish hip fracture patients between 2004 and 2018. We examined the association between comorbidity and infection on relative scale and presented both short- and long-term cumulative incidences of any and specific infections after hip fracture surgery.

Method

Setting and data sources

Danish residents (approximately 5.9 million in 2022) have access to universal tax-supported healthcare from general practitioners and hospitals.

Following registries were used in this cohort study: the Danish Multidisciplinary Hip Fracture Registry (DMHFR), the Danish Civil Registration System, the Danish National Patient Registry, the Danish National Prescription Registry, and the Population Education Registry. The DMHFR contains information on in-hospital quality indicators, prognostic factors, and outcomes for all Danish patients aged ≥ 65 years with hip fracture since 2004. The DMHFR only includes patients at the first surgery for a first-time unilateral hip fracture [14, 15]. Registration to the DMHFR is mandatory for all hospitals. The Danish Civil Registration System assigns a unique personal identifier to all Danish residents, enabling linkage of data from numerous population-based medical registries on an individual level and tracking of vital status and migration [16]. The Danish National Patient Registry has recorded discharge dates and diagnoses from all hospitalizations since 1977 and from all outpatient specialist clinics and emergency department contacts since 1995 [17]. The International Classification of Diseases 10th Edition (ICD-10) has been used since 1994 [17]. The Danish National Prescription Registry contains ATC-codes and dates on all reimbursed medication dispensed from all community pharmacies since 2004 [18]. The Population Education Registry contains information on education level for education completed in Denmark or, if completed abroad, self-reported and analogous to existing Danish educations [19].

Study cohort

The cohort of 92,600 incident hip fracture patients aged ≥ 65 treated surgically with total/hemi-arthroplasty or internal fixation between January 2004 and December 2018 was identified from the DMHFR.

Comorbidity

Comorbidity was measured with the Charlson comorbidity index (CCI) score [20]. The Danish National Patient Registry was used to identify comorbidity diagnoses included in the CCI for the 10 years preceding date of surgery for the hip fracture. A fixed lookback period of 10 years was chosen to ensure equal lookback periods for all patients and avoid major changes in the registration practice, particularly regarding the implementation of ICD-10 diagnosis codes in place of ICD-8 in 1994 [17]. To calculate the CCI score for each patient, diagnoses from both hospitalizations and outpatient clinic contacts were used. Emergency department contacts were disregarded due to assumed lower validity of the diagnoses, as these may reflect working diagnoses or minor disease not eligible for further hospital admission. Three levels of comorbidity were defined: none (CCI score = 0), for patients with no previous record of the diseases included in the CCI; moderate (CCI score = 1–2); and severe (CCI score ≥ 3).

Infections

The primary outcome was a composite endpoint of any hospital-treated infection. Secondary outcomes were hospital-treated pneumonia, hospital-treated UTI, hospital-treated sepsis, and reoperation due to SSI. A composite endpoint of any hospital- or community-treated infection was included to estimate the risk of any infection in need of treatment, while avoiding issues of time-dependent bias because patients are not eligible for community-based treatment while hospitalized for hip fracture.

Infections were identified using ICD-10 codes in the DNPR for primary and secondary discharge diagnoses among hospitalized patients or patients with an outpatient clinic or emergency department contact. Any hospital-treated infection included pneumonia, UTI, sepsis, and other infections, such as appendicitis, erysipelas, and abscesses. Reoperation due to SSI was defined by combining Nordic Medico-statistical Committee (NOMESCO) surgery codes for reoperation in the hip or thigh and ICD codes for infection or wound rupture. Community-treated infections were identified from the Danish National Prescription Registry using the date of the first dispensing of any antimicrobial drug after hip fracture surgery, including systemic and local antibacterial, antiviral, antimycotic, and antiparasitic drugs [18]. For sensitivity analysis, community-treated infection was also defined using only first dispensing of any systemic antibacterial drug, as the remaining antimicrobial treatments might be used for rare or very mild infections.

Variables

We measured the following variables at the date of admission for hip fracture:

1) Patient sex and age were retrieved from the Danish Civil Registration System [16]. Age was categorized into four age groups: 65–74 years, 75–84 years, 85–94 years, and ≥ 95 years.
2) Information on surgery year, body mass index (BMI), fracture type, and surgery type were collected from the DMHFR. Surgery year was categorized into the following 5-year periods: 2004–2008, 2009–2013, and 2014–2018. BMI categories were defined as underweight (< 19), normal weight (19–24.9), overweight (25–29.9), obese (≥ 30), outliers (BMI < 10 or > 50), or missing.
3) Data on education were retrieved from the National Population Education Registry [19] and defined as none or missing, primary and lower secondary education, upper secondary education, academy progression program education, professional or non-academic bachelor's degree, and university degree (bachelor's, master's, or doctoral degree).
4) Surgery delay and length of hospital stay were obtained from the DMHFR and the Danish National Patient Registry.

Diagnosis codes, surgery codes, and prescription codes for the definition of comorbidity, infections, and other variables are provided in Online Resource 1.

Statistical analysis

Characteristics of the study cohort was tabulated by comorbidity level.

The analysis was performed for the defined primary outcome and each of the defined secondary outcomes. In each analysis, patients were followed from date of hip fracture surgery and up to 1 year after date of surgery until outcome of interest, death, migration ($n = 28$), or 31 December 2018, whichever came first. Hence, there was no minimum follow-up period. Analyses were done at 0–30 days and 0–365 days.

Cumulative incidence of infection was computed, treating death as a competing risk [21]. Incidence rates (IRs) per 10 person-years were computed as well, both crude and standardized to age, sex, and surgery year of the overall study cohort.

Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using Cox proportional regression analysis comparing patients with moderate and severe comorbidity to patients with no comorbidity. Patients who experienced the competing event of death were censored and, thus, only contributed to risk time while alive and at risk of infection [21]. HRs were adjusted for age, sex, and surgery year, as these were identified as possible confounders by means of directed acyclic graphs [22]. Variables were considered confounders if associated to both comorbidity and infection, without being a mediator (e.g., medication use, surgery type) on the causal path from comorbidity to infection. Assumption of proportionality in the Cox models was evaluated by log(-log) plot and found acceptable, as curves were parallel with approximately constant vertical distance and without overcrossing. As hazard rate equivalates to the risk of an event occurring at a certain timepoint without the event or competing risk having occurred beforehand, in this study, HR is interpreted as a relative instantaneous risk [23].

To evaluate possible effect measure modification, HRs for any hospital-treated infection were calculated while stratifying for age, sex, and surgery year. To evaluate unmeasured confounding by socioeconomic position and nutritional status, HRs for any hospital-treated infection were calculated while adjusting for BMI categories and/or education. Missing values for BMI and education were assumed to be missing at random and were either relabeled as "unknown" or handled in a complete-case analysis. [24]

Analysis was performed using R software (version 2022.02.1).

This paper follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [25] and the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines for cohort studies [26].

Ethical approval and patient consent

The study was reported to the Danish Data Protection Agency through registration at Aarhus University (record number: AU-2016-051-000001, sequential number 880).

Patient consent is by Danish law not required for registry-based studies.

Results

Characteristics of the study cohort

A total of 92,600 patients underwent surgery for hip fracture; 71% were women and the median age was 83 years. The prevalence of none, moderate, and severe comorbidity was 40%, 40%, and 19%, respectively. The most frequent comorbidities contributing to the CCI score were cerebrovascular disease (e.g., stroke), any solid tumor, and chronic pulmonary disease.

Patients with no comorbidity were more likely to be women, age > 85 years, and to have had surgery in the earlier period than patients with severe comorbidity. Length of hospital stay and surgery delay increased slightly with comorbidity. Distributions of BMI categories, education level, fracture, and surgery type were similar in the three comorbidity groups (Table 1).

Infections

The cumulative incidence of any hospital-treated infection increased with increasing comorbidity level. The cumulative incidence of any hospital-treated infection within 0–30 days of surgery was 12.6% among patients with no comorbidity, 16.2% among patients with moderate comorbidity, and 19.5% among patients with severe comorbidity. Within 1 year after surgery, the cumulative incidence of any hospital-treated infection was 22.2% among patients with no comorbidity, 29.8% among patients with moderate comorbidity, and 36.6% among patients with severe comorbidity. The cumulative incidence increased with comorbidity at both 0–30 days and 0–365 days of follow-up for all secondary outcomes (Fig. 1, Online Resource 2).

Crude and standardized IRs are presented in Online Resource 2 and follow the pattern seen for cumulative incidence.

Compared to patients with no comorbidity, patients with moderate and severe comorbidity had adjusted HRs for any hospital-treated infection of 1.3 (95% CI: 1.3–1.4) and 1.6 (95% CI: 1.5–1.7), respectively, within 30 days after surgery, and 1.4 (95% CI: 1.4–1.5) and 1.9 (95% CI: 1.9–2.0), respectively, within 1 year after surgery.

A similar pattern of association was observed between comorbidity and secondary outcomes (Fig. 2, Fig. 3, and Online Resource 2). The strongest association was observed for sepsis, whereas the weakest association was observed for reoperation due to SSI.

Additional analyses

The cumulative incidence and IRs of any hospital-treated infection varied slightly but increased with increasing comorbidity level regardless of age, sex, and surgery year, and the HRs pointed in the same direction as those obtained in the main analyses. The association between comorbidity and any hospital-treated infection was more pronounced in younger patients than in older patients (Online Resource 2).

The HRs for any hospital-treated infection did not change substantially after additional adjustment for education and/or BMI (Online Resource 2).

Defining community-treated infection using only systemic antibacterial drugs in sensitivity analysis, cumulative incidences of any hospital- or community-treated infection decreased slightly, and HRs were comparable to those of the of main analysis (Online Resource 2).

Discussion

We found that comorbidity is a risk factor for infection up to 1 year after surgery regardless of age, sex, and surgery year. The risk of infection was high regardless of comorbidity, but especially high for any hospital-treated infection and any hospital- or community-treated infection among patients with severe comorbidity within 1 year.

Comparison to existing research

Our findings for pneumonia, UTI, and sepsis were similar or lower than incidences reported in previous studies. As such, studies from the Netherlands and Sweden reported incidences of 9.7% and 8.9%, respectively, for UTI and 9.5% and 4.5%, respectively, for pneumonia within the initial hospitalization related to the hip fracture [2, 11]. The 30-day incidence of sepsis among patients with hip fracture was 2.4% in a US study [3]. Differences may be due to variations in follow-up (30 days vs. in-hospital), accounting for competing risk, healthcare setting, and case-mix, but also variations in the definition of infection and inclusion criteria for the study population (e.g., all hip fracture patients vs. hip fracture patients treated surgically, age limit). In contrast, at more long-term follow-up, we found a 1-year incidence of pneumonia of 11.9%, which is notably higher than the incidence of 5.3% reported in the Swedish study [11]. However, the Swedish study counted only pneumonia at readmissions as outcome while we also included pneumonia diagnosed within the index hospitalization as outcome.

Few studies have examined the association between comorbidity and risk of infection during hospitalization for hip fracture or 30 days after. A case-control study of 9806 Chinese patients with hip fracture [9] found an association between comorbidity measured by CCI and the risk of in-hospital infection, including pneumonia, UTI, SSI, and other infections. An association has also been reported between the American Society of Anesthesiologists (ASA) score

Table 1 Population characteristics

	Overall	Comorbidity level (CCI score*)		
		None (0)	Moderate (1–2)	Severe (≥ 3)
Sex				
Female	65,813 (71.1%)	28,697 (76.8%)	26,318 (70.5%)	10,798 (60.3%)
Male	26,787 (28.9%)	8649 (23.2%)	11,034 (29.5%)	7104 (39.7%)
Age				
65–74 years	18,191 (19.6%)	7556 (20.2%)	6751 (18.1%)	3884 (21.7%)
75–84 years	35,744 (38.6%)	13,543 (36.3%)	14,581 (39.0%)	7620 (42.6%)
85–94 years	34,376 (37.1%)	14,070 (37.7%)	14,367 (38.5%)	5939 (33.2%)
≥ 95 years	4289 (4.6%)	2177 (5.8%)	1653 (4.4%)	459 (2.6%)
Median (interquartile range)	83 (77, 89)	84 (77, 89)	84 (77, 89)	82 (76, 87)
Surgery year				
2004–2008	31,675 (34.2%)	13,643 (36.5%)	12,737 (34.1%)	5295 (29.6%)
2009–2013	31,702 (34.2%)	12,581 (33.7%)	12,890 (34.5%)	6231 (34.8%)
2014–2018	29,223 (31.6%)	11,122 (29.8%)	11,725 (31.4%)	6376 (35.6%)
Comorbidity level (CCI score)				
None (0)	37,346 (40.3%)	-	-	-
Moderate (1–2)	37,352 (40.3%)	-	-	-
Severe (≥ 3)	17,902 (19.3%)	-	-	-
BMI category				
<19	13,184 (14.2%)	5137 (13.8%)	5592 (15.0%)	2455 (13.7%)
19–24.9	35,349 (38.2%)	14,822 (39.7%)	14,151 (37.9%)	6376 (35.6%)
25–29.9	17,991 (19.4%)	7365 (19.7%)	6998 (18.7%)	3628 (20.3%)
> 30	5129 (5.5%)	1935 (5.2%)	1953 (5.2%)	1241 (6.9%)
< 10 or > 50	160 (0.2%)	55 (0.2%)	63 (0.2%)	42 (0.2%)
Missing	20,787 (22.5%)	8032 (21.5%)	8595 (23.0%)	4160 (23.2%)
Education level				
Primary and lower secondary education	43,259 (46.7%)	17,036 (45.6%)	17,459 (46.7%)	8764 (49.0%)
Upper secondary education	20,909 (22.6%)	7854 (21.0%)	8440 (22.6%)	4615 (25.8%)
Academy progression program education	1386 (1.5%)	538 (1.4%)	581 (1.6%)	267 (1.5%)
Professional or non-academic bachelor's degree	5838 (6.3%)	2413 (6.5%)	2299 (6.2%)	1126 (6.3%)
University degree	2001 (2.2%)	800 (2.1%)	786 (2.1%)	415 (2.3%)
Missing or no education	19,207 (20.7%)	8705 (23.3%)	7787 (20.9%)	2715 (15.2%)
Diseases				
Myocardial infarction	4982 (5.4%)	0 (0.0%)	2146 (5.8%)	2836 (15.8%)
Chronic pulmonary disease	11,565 (12.5%)	0 (0.0%)	6191 (16.6%)	5374 (30.0%)
Connective tissue disease	4414 (4.8%)	0 (0.0%)	2502 (6.7%)	1912 (10.7%)
Congestive heart failure	8450 (9.1%)	0 (0.0%)	3680 (9.9%)	4770 (26.7%)
Peripheral vascular disease	7392 (8.0%)	0 (0.0%)	3399 (9.1%)	3993 (22.3%)
Cerebrovascular disease	16,905 (18.3%)	0 (0.0%)	10,063 (26.9%)	6842 (38.2%)
Dementia	8,845 (9.6%)	0 (0.0%)	5762 (15.4%)	3083 (17.2%)
Ulcer disease	5159 (5.6%)	0 (0.0%)	2602 (7.0%)	2557 (14.3%)
Mild liver disease	1052 (1.1%)	0 (0.0%)	398 (1.1%)	654 (3.7%)
Diabetes, uncomplicated	7939 (8.6%)	0 (0.0%)	3,121 (8.4%)	4,818 (26.9%)
Diabetes, complicated	4422 (4.8%)	0 (0.0%)	847 (2.3%)	3575 (20.0%)
Hemiplegia	230 (0.3%)	0 (0.0%)	49 (0.1%)	181 (1.0%)
Moderate to severe renal disease	3,619 (3.9%)	0 (0.0%)	511 (1.4%)	3,108 (17.4%)
Any solid tumor	13,735 (14.8%)	0 (0.0%)	5153 (13.8%)	8582 (47.9%)
Leukemia	460 (0.5%)	0 (0.0%)	149 (0.4%)	311 (1.7%)
Lymphoma	810 (0.9%)	0 (0.0%)	229 (0.6%)	581 (3.3%)

Table 1 (continued)

	Overall	Comorbidity level (CCI score*)		
		None (0)	Moderate (1–2)	Severe (≥ 3)
Moderate to severe liver disease	397 (0.4%)	0 (0.0%)	0 (0.0%)	397 (2.2%)
Metastatic solid tumor	1,404 (1.5%)	0 (0.0%)	0 (0.0%)	1404 (7.8%)
HIV/AIDS	22 (0.0%)	0 (0.0%)	0 (0.0%)	22 (0.1%)
Fracture type				
Fracture of head and neck of femur	49,120 (53.0%)	19,961 (53.5%)	19,705 (52.8%)	9454 (52.8%)
Pertrochanteric fracture of femur	36,911 (39.9%)	14,714 (39.4%)	15,023 (40.2%)	7174 (40.1%)
Subtrochanteric fracture of femur	6569 (7.1%)	2671 (7.2%)	2624 (7.0%)	1274 (7.1%)
Surgery type				
Arthroplasty	29,131 (31.5%)	11,844 (31.7%)	11,725 (31.4%)	5562 (31.1%)
Osteosynthesis	63,469 (68.5%)	25,502 (68.3%)	25,627 (68.6%)	12,340 (68.9%)
Surgery delay time, hours				
Median (interquartile range)	21 (14, 31)	21 (14, 30)	21 (14, 32)	22 (14, 33)
Length of stay, days				
Median (interquartile range)	8 (5, 13)	8 (5, 12)	8 (5, 13)	9 (5, 14)

Values are *n* (%) unless otherwise noted. Abbreviations: *CCI* Charlson comorbidity index, *BMI* body mass index

*Variables collected at baseline, except comorbidity burden and diseases (measured prevalence within 10 years prior to hip fracture surgery)

and pneumonia and SSI within the immediate few weeks after surgery [2, 10, 11] and within 1 year of hip fracture [11]. The ASA score, intended for pre-surgical anesthesia risk evaluation, is frequently used in health sciences as a proxy measure of comorbidity or overall health status [27]. Although both the ASA score and CCI are associated with mortality up to 1 year after hip fracture [28, 29], the interchangeability of the two measures is uncertain in regard to the risk of infection.

Our study extended available knowledge by finding a strong association between CCI and infection risk up to 1 year after hip fracture surgery.

Potential mechanisms and clinical implications

In our study, the CCI was used as a measure of comorbidity level. However, it remains important to consider the distribution of the individual comorbidities within the CCI levels, as the individual diseases might differ in association to infection risk in hip fracture patients. For example, the association between chronic pulmonary disease and pneumonia or diabetes and poor wound healing is well established, and the underlying mechanisms appear biologically plausible. Direct effects of history of myocardial infarction on infection risk seem less obvious but may also appear plausible if myocardial infarction is considered a marker of frailty in these patients. Frailty is strongly bidirectionally associated with comorbidity and is a risk factor for adverse outcomes in the older population [30].

Our study showed a clear increase in infection risk with increasing levels of comorbidity, and although guidelines exist for in-hospital care of hip fracture patients, they do not take comorbidity level into consideration [12, 13]. Comorbidity-related inequality in the quality of in-hospital care of hip fracture patients has been reported previously. Thus, Danish hip fracture patients with a high level of comorbidity are less likely to fulfill all relevant in-hospital treatment quality indicators, such as early mobilization and pain assessment [31]. Sufficient pain assessment and management are closely related to early mobilization of patients [32], and not regaining pre-fracture mobility is a strong risk factor for infection within 30 days of hip fracture surgery [33]. In contrast, opioid overuse is of concern because opioids are suspected to have immune-modulating effects [34].

Furthermore, though the timing, dosage, and type of prophylactic antibiotics in hip fracture patients have been of interest in research, clinical recommendations only exist on the national or local level [12, 13, 35] and adherence to these guidelines has been lacking [35]. Whether comorbidity-related inequality in proper infection prophylaxis exists among hip fracture patients or hip fracture patients could benefit from comorbidity-tailored prophylactic use of antibiotics or the use of pre-surgery regimens to eliminate nasal carriage of *Staphylococcus aureus*, a major cause of SSIs, is unclear [36].

Length of hospital stay has also been of interest in research and has been severely reduced in hip fracture

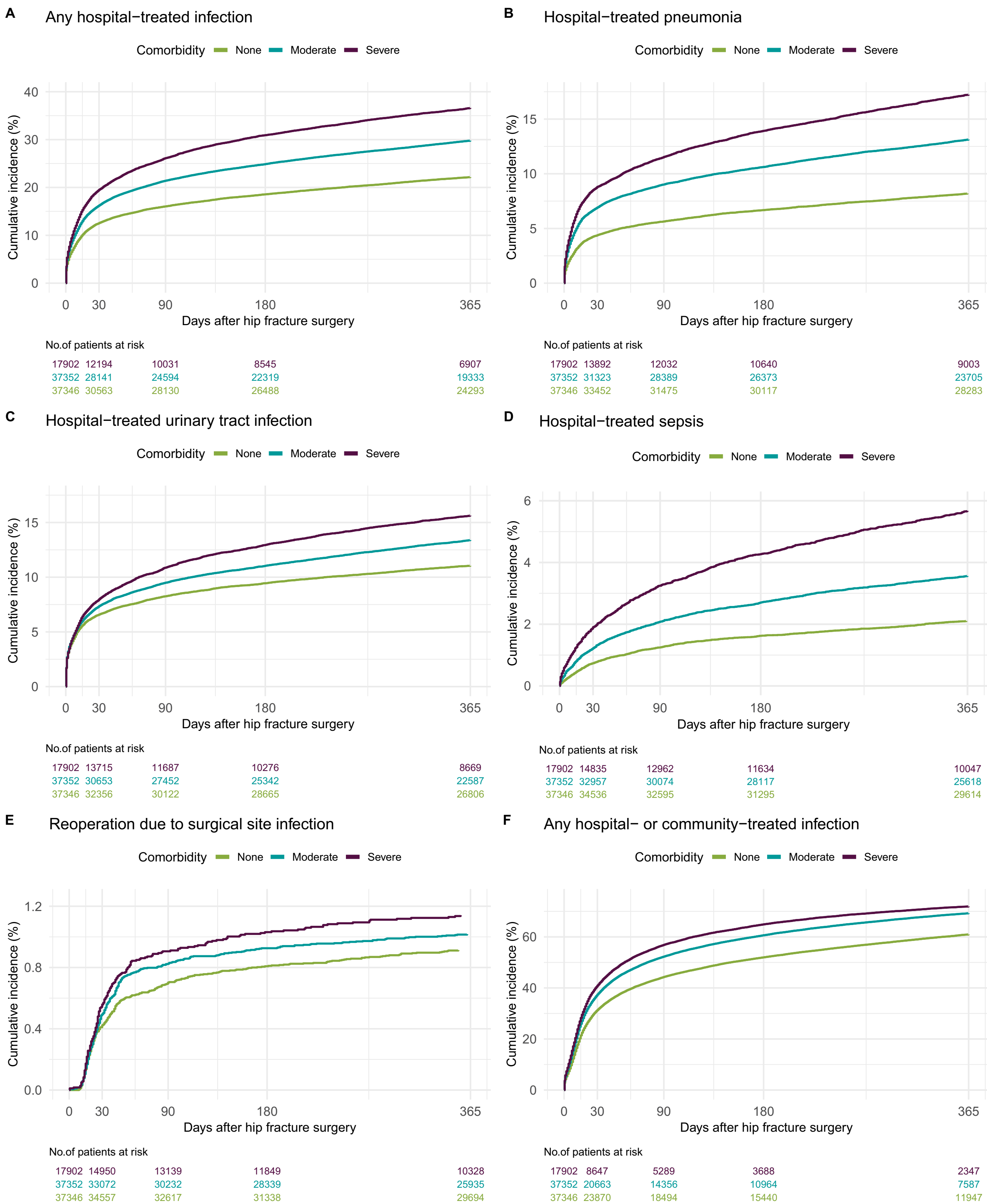

Fig. 1 Cumulative incidence curves for each of the six outcome measures (see **A**–**F**) at 0–365-day follow-up, by comorbidity level (CCI score), considering death a competing risk. Number of patients at risk at 0, 30, 90, 180, and 365 days of follow-up

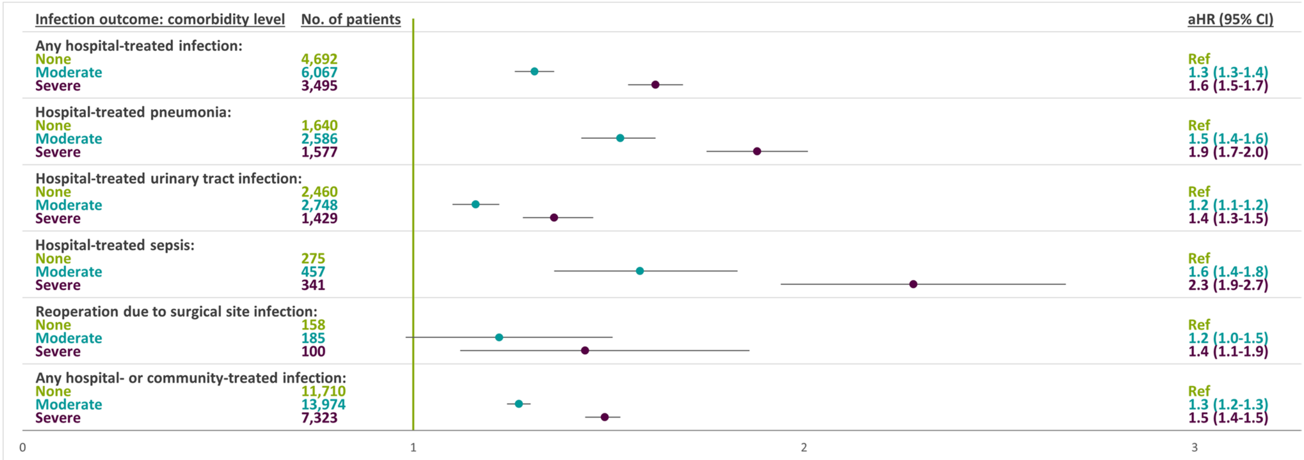

Fig. 2 Hazard ratios and number of patients with outcome for all six outcome measures at 0–30-day follow-up, by comorbidity level (CCI score). Hazard ratios with no comorbidity as reference and adjusted for age, sex, and surgery year. Abbreviations: adjusted hazard ratio (aHR); 95% confidence interval (95% CI)

patients across the world [37, 38]. However, in different health care settings, short length of stay has been associated with both an increased and reduced risk of mortality in hip fracture patients [39]. In our study, the median length of stay was 8 days for patients with none and 9 days for patients with severe comorbidity. It remains unknown whether patients with severe comorbidity could benefit from shorter length of stay if they are discharged to a well-functioning home setting or from elongated length of stay to optimize other risk factors for infection the patient may have.

In the stratified analysis, we observed an association between comorbidity level and any hospital-treated infection decreased with increasing age. Possible explanations include (1) age is an effect modifier weakening the effects of comorbidity as a risk factor. (2) The severity of the measured comorbidities decreases with increasing age or misclassification of comorbidity status differs across age groups. (3) Clinical decisions associated with increasing age and comorbidity status, e.g., if older comorbid patients are at higher risk of receiving community-based or palliative care, rather than being admitted to hospital compared to patients of younger age and with no comorbidity. (4) Competing risk by death increase with age and comorbidity status. In clinic, comorbidity status remains important to consider in infection risk evaluation across all age groups, but especially

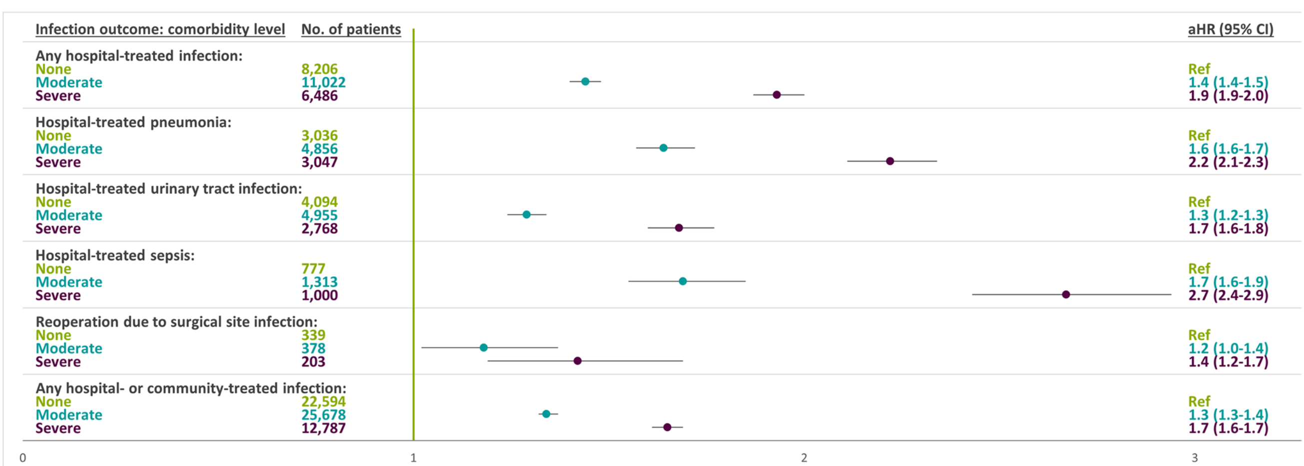

Fig. 3 Hazard ratios and number of patients with outcome for all six outcome measures at 0–365-day follow-up, by comorbidity level (CCI score. Hazard ratios with no comorbidity as reference and adjusted for age, sex, and surgery year. Abbreviations: adjusted hazard ratio (aHR); 95% confidence interval (95% CI)

among the youngest patients. Potential explanations for the increased risk of infection among comorbid patients up to 1 year compared with up to 30 days are more likely to be related to patient characteristics and the organization of patient care at home than hip fracture treatment. When admitted to hospital, patients are in close contact with medical staff, more conveniently enabling the optimization of comorbidity treatment, the patient's general status, and vigilance towards early signs of infection. This does not apply to the home setting. As such, there is no clear recommendation for the prevention of complications in the community setting [12, 13]. Though, by law, Danish patients must be offered free-of-charge rehabilitation if needed upon discharge from hospital [40], it is unknown whether hip fracture patients attend or even complete rehabilitation and whether this differs by comorbidity level. Implementation of geriatric-, nurse-, or general practitioner-based follow-up visits after discharge has been investigated in a few single hospitals, and the results have been inconclusive [41, 42]. More studies are needed in order to determine whether patients with comorbidity may benefit from closer contact by health professionals with the aim of improving prophylaxis, early diagnosis, and treatment of infection in the community setting.

Considering the high incidences of infection and strong association between comorbidity level and infection as found in our study, more tailored patient-specific guidelines taking the level of comorbidity into account could potentially improve in-hospital outcomes, but also up to the first postoperative year.

Methodological considerations

Our study has limitations.

First, the completeness of the registration of patients with hip fracture in the DMHFR has not been assessed in a peer-review publication. In Denmark, all patients with hip fracture are treated at public hospitals and a registration to the DMHFR is mandatory via the Danish National Patient Registry since hospitals are reimbursed based on registration of diagnosis and surgery codes for hip fracture treatment. Thus, completeness of registration is considered to be high. We cannot, however, exclude a possibility that a few patients are not registered.

Second, we cannot exclude possible bias due to misclassification. Though the positive predictive value (PPV) for the record of hip fracture event in the DMHFR is 100% [15], the PPV for the ICD codes used for the assessment of CCI ranges from 82 to 100% [43], and a study conducted on Danish cancer patients found a PPV of 98% for any infection, 93% for pneumonia, and 84% for sepsis using primary diagnoses of the Danish National Patients Registry [44]. However, as information regarding the diagnoses is collected routinely and prospectively regardless of the outcome examined in this study, the risk of differential misclassification is suspected to be very low.

Third, to estimate the CCI score, only diagnoses recorded during hospital contacts were used because Danish primary care data do not include diagnosis codes. We would have to rely on other proxies for comorbidity diagnosis in general practice, such as prescription records. Consequently, less severe conditions treated by general practitioners were not included in the comorbidity score. The Danish National Prescription Registry only records prescriptions on medications dispensed in community pharmacies; as such, there are no available data on the use of antimicrobial drugs in-hospital.

Lastly, we cannot eliminate the risk of unmeasured confounding because we lacked data on lifestyle factors. In addition, as comorbidity, hip fracture, and infection may share risk factors, collider bias could potentially have an impact on our estimates [45]. The crude and adjusted HRs of the main analysis differed only slightly; also, the supplementary HRs adjusted for education and BMI did not differ substantially from the adjusted HRs in the main analysis. Therefore, we consider unmeasured confounding and collider bias to be minor.

Regardless, the association of comorbidity and infection may differ in other populations with different case-mix, health care system, treatment, and rehabilitation of hip fracture patients.

Conclusion

Among patients with hip fracture, the risk of infection is high regardless of comorbidity, but especially high among patients with severe comorbidity and within 1 year after surgery. In our cohort, comorbidity was an important predictor of risk of infection up to 1 year after surgery regardless of age, sex, or surgery year.

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Data availability To protect the privacy of patients, it is by Danish law prohibited to make individual level data publicly available.

Declarations

Ethical approval and patient consent The study was reported to the Danish Data Protection Agency through registration at Aarhus University (record number: AU-2016-051-000001, sequential number 880). Patient consent is by Danish law not required for registry-based studies.

Conflict of interest N. R. G., C. V. G., R. G. H. H. N., H. T. S., and A. B. P. report no conflicts of interest. C. V. received travel expenses from Stryker with no relevance to the present study. The results from this paper were presented at the following meetings: The 11th International Congress of Arthroplasty Registries, Ireland, September 2022; The Annual Congress of the Danish Orthopaedic Society, Denmark, November 2022; The 5th Annual Research Meeting at Department of Clinical Medicine, Aarhus University, Denmark, November 2022.

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