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Clinical Epidemiology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/dcle20

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To cite this article: Cecilia Majlund Hansen, Nadia R Gadgaard, Christina Vandenbroucke-Grauls, Nils P Hailer & Alma Becic Pedersen (2025) Interaction Between Multimorbidity and Hip Fracture Surgery Leads to Excess Risk of Infection: A Danish Registry-Based Cohort Study of 92,599 Patients With Hip Fracture, Clinical Epidemiology, , 167-176, DOI: 10.2147/CLEP.S507252

To link to this article: https://doi.org/10.2147/CLEP.S507252

Published online: 24 Feb 2025.

Clinical Epidemiology

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ORIGINAL RESEARCH

Interaction Between Multimorbidity and Hip Fracture Surgery Leads to Excess Risk of Infection: A Danish Registry-Based Cohort Study of 92,599 Patients With Hip Fracture

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Purpose: Infection in general is a frequent and serious complication after hip fracture (HF) surgery. Multimorbidity in HF patients is associated with elevated infection risk. It remains unclear whether multimorbidity interacts with HF surgery to increase infection risk beyond their individual effects.

Methods: Using Danish registries, we identified 92,599 patients ≥65 years surgically treated for HF 2004 to 2018 and an age- and sex-matched comparison cohort from the background population without HF (n=462,993). Multimorbidity was defined using the Charlson Comorbidity Index in categories no, moderate, or severe. We computed incidence rates (IR) of any kind of hospital-treated infection within 1 month and 1 year with 95% confidence intervals and estimated the attributable proportion (in %) based on differences in IRs.

Results: The IR of infection within 1 month was 181 (176–186) per 100 person years in HF patients with no multimorbidity and 9 (95% CI 8–9) in the comparison cohort with no multimorbidity. The IRs were 240 (234–246) and 302 (291–313) in HF patients with moderate and severe multimorbidity compared with 17 (16–18) and 31 (30–33) in the comparison cohort with same multimorbidity level. The attributable proportion indicates that 21% and 33% of the IR among HF patients with moderate and severe multimorbidity, respectively, was explained by interaction. Similar interactions were observed within 1 year.

Conclusion: Multimorbidity and HF surgery interact synergistically, which substantially increases the infection risk. The interaction effect increased with multimorbidity level. Our findings highlight the potential benefits of implementing more targeted and personalized preventive initiatives for multimorbid patients.

Keywords: comorbidity, epidemiology, hip fracture, infection, interaction, multimorbidity

Introduction

Hip fracture is a major public health concern worldwide.[1] According to SCOPE 2021 (ScoreCard for Osteoporosis in Europe) there were more than 826,000 hip fractures in Europe in 2019, and Denmark has one of the highest incidences of hip fracture.[2,3] For the population aged 65 years or older, hip fracture is the dominant cause of trauma-related deaths and 50% of survivors never reach their previous functional level.[2,4] Almost 10% of the patients die within the first month, while one-year cumulated mortality ranges from 11.8% to 52.1% depending on patient characteristics including multimorbidity.[5,6] Prevalence of multimorbidity among hip fracture patients has been increasing and today more than 50% of hip fracture patients live with at least one chronic disease.[5,7] Multimorbidity is a risk factor for both hip fracture and subsequent mortality and for infection after hip fracture surgery.[5–7]

Received: 18 November 2024
Accepted: 15 February 2025
Published: 24 February 2025

Infection, such as pneumonia and urinary tract infection, is a common complication after hip fracture surgery. Approximately 15% of Danish hip fracture patients sustain an infection within the first 30 days after surgery and 30-day mortality is 2-fold higher in hip fracture patients who develop infection compared to patients without.[8,9] Pneumonia is the second leading cause of death among hip fracture patients.[10] Multimorbidity interacts with hip fracture surgery to increase the risk of mortality and complications such as venous thromboembolism, stroke, and myocardial infarction beyond the independent effects of hip fracture surgery and multimorbidity.[11,12,13]

However, it remains unclear whether there is a synergistic effect between multimorbidity and hip fracture surgery that increases the risk of infection more than what is explained by their additive effects. This knowledge would contribute to identifying subgroups of hip fracture patients that are particularly prone to sustaining an infection and thereby find areas for intervention to reduce the risk of infection and mortality. Therefore, we investigated the interaction effect between multimorbidity and hip fracture surgery on infection incidence within 1 month and 1 year of surgery comparing hip fracture patients and individuals from the background population with and without multimorbidity.

Methods

Design and Setting

In this matched population-based cohort study we used prospectively collected data from Danish nationwide medical databases. Denmark is a welfare state with 5.9 million residents and tax-supported healthcare offering free access to healthcare services including general practice and hospitals for all Danish residents.[14]

Data Sources

All Danish residents are assigned a unique 10-digit identifier at birth or immigration, which enables individual level linkage of data between multiple databases.

The Danish Civil Registration System holds data on date of birth, date of death, sex, and migration status since 1968.[15]

The Danish Multidisciplinary Hip Fracture Registry (hip fracture registry) was implemented in 2003 with the aim to monitor and improve quality of in-hospital treatment of patients 65 years of age or older undergoing hip fracture surgery.[2] Patients and their clinical data are included through discharge diagnosis codes (S72) and surgery codes (NFJ and NFB) recorded during the same hospitalization.

The Danish National Patient Registry (patient registry) holds data on all somatic hospital admissions to Danish hospitals since 1977 and outpatient clinic visits since 1995.[16] Discharge diagnoses are coded using the International Classification of Disease 10th revision (ICD-10).

Hip Fracture Cohort and Comparison Cohort

A hip fracture cohort of all patients undergoing surgery due to a first-time unilateral hip fracture in the period from 2004 to 2018 was identified in the hip fracture registry.

A comparison cohort from the general population without hip fracture was identified in the Civil Registration System and the hip fracture registry to calculate background risk of infection. For each hip fracture patient, 5 comparators were randomly sampled with replacement. Thus, an individual sampled as comparator could serve as a match for more than one hip fracture patient. Index date for comparators was the surgery date of the hip fracture patient whom they were matched to. Comparators were matched on age, sex, being alive and hip fracture-free on index date, meaning they could be included in the hip fracture cohort in the future. In total, 333,012 individuals were sampled as comparators, of whom 242,935 served as comparators only once. The remaining comparators were sampled more than ones and 120 hip fracture patients had the same comparator matched to them more than once. Less than five individuals were excluded from both cohorts because no eligible match was found or because of incorrect registration of infection or date of death, resulting in a hip fracture cohort of 92,599 patients and a comparison cohort of 462,993 individuals.

Multimorbidity

The exposure was multimorbidity level defined using the Charlson Comorbidity Index (CCI) which includes 19 defined chronic somatic comorbid diseases.[17,18] Information on hospital diagnoses of these diseases was collected from the patient registry during the 10 years prior to index date. All individuals were categorized by multimorbidity level into groups of no (CCI score = 0), moderate (CCI score = 1–2), or severe (CCI score = ≥ 3) multimorbidity.

Infection

The outcome of hospital-treated infection was identified through primary and secondary discharge diagnoses as recorded in the patient registry, including all hospital admissions, outpatient clinic visits, and emergency room visits.

Variables

Age, sex, and vital status were obtained from the Civil Registration System. Information on year of surgery was obtained from the hip fracture registry. Diagnosis codes used for definition of multimorbidity and infection are provided in Table S1 and Table S2.

Statistical Analysis

Descriptive statistics of the hip fracture cohort and the comparison cohort were tabulated overall and by multimorbidity level. Hip fracture patients and comparators were followed for outcome of any hospital-treated infection from index date until end of follow-up period (0–30 days or 0–365 days), death, emigration, or end of study (December 31st, 2018), whichever came first.

Both cohorts were divided into three multimorbidity levels. Thus, we had three hip fracture sub-cohorts with no, moderate, and severe multimorbidity and three comparison sub-cohorts with no, moderate, and severe multimorbidity.

We calculated incidence rates per 100 person years with 95% confidence intervals (CI), both crude and standardized by sex, age in 5-year intervals, and index year in 5-year intervals, overall and for all six sub-cohorts.

Multivariate Cox regression was used to compute hazard ratios (HR) with 95% CI adjusting for age, sex, and index year. Two Cox regression analyses were conducted:

1) Comparing the hip fracture cohort to the comparison cohort overall and within multimorbidity sub-cohorts. Thus, comparing hip fracture patients with no, moderate and severe multimorbidity respectively to comparators with the same levels of multimorbidity.

2) Using the comparison cohort with no hip fracture and no multimorbidity as a reference, we computed HRs for the five other sub-cohorts (comparison cohort with moderate and severe multimorbidity and hip fracture cohort with no, moderate and severe multimorbidity).

Assumption of proportionality in the Cox models was checked visually using log(-log) plots and found acceptable.

To examine the presence of interaction between hip fracture surgery and multimorbidity on the risk of infection both on absolute and relative scale, two different interaction measures were calculated.

As a measure of interaction on absolute scale, the interaction contrast was calculated based on differences in incidence rates. The interaction contrast denotes the excess incidence rate of infection among hip fracture patients with multimorbidity that is left when subtracting incidence rates attributed to background risk, to hip fracture surgery and to multimorbidity. Thus, the interaction contrast is the absolute excess risk that is attributed to the interaction itself.

$$\begin{aligned} \textit{Interaction contrast} = {} & IR_{\textit{hip fracture with multimorbidity}} - IR_{\textit{comparison without multimorbidity}} \\ & - \left(IR_{\textit{hip fracture without multimorbidity}} - IR_{\textit{comparison without multimorbidity}}\right) \\ & - \left(IR_{\textit{comparison with multimorbidity}} - IR_{\textit{comparison without multimorbidity}}\right) \end{aligned}$$

Since the interaction contrast is an incidence rate, which is not intuitively interpreted clinically, the interaction contrast is transformed to an attributable proportion to present the percentages of infections explained by the interaction effect between hip fracture surgery and multimorbidity. This is done by dividing the interaction contrast by the incidence rate of infection for the group "hip fracture patients with multimorbidity".

https://doi.org/10.2147/CLEP.S507252

$$Attributable\ fraction = (HR_{hip\ fracture\ with\ multimorbidity} - HR_{hip\ fracture\ without\ multimorbidity} - HR_{comparison\ with\ multimorbidity} + 1)/HR_{hip\ fracture\ with\ multimorbidity}$$

As a measure of interaction on relative scale, the attributable fraction (in %) was calculated based on HRs.[19,20] The attributable fraction can be interpreted as a theoretical estimation of how much the HR could be reduced if the interaction between hip fracture and multimorbidity was not present. Thus, the attributable fraction is the relative excess risk that is attributable to the interaction itself.

All analyses were performed for the follow-up period of 1 month (0–30 days) and 1 year (0–365 days).

The analysis was performed using R software (version 4.2.2).

The reporting of this study follows the Reporting of studies Conducted with Observational Routinely collected Data (RECORD) guidelines.[21]

Results

Characteristics of the Cohorts

The median age was 83 years in both the hip fracture and comparison cohort but varied from 82 to 85 years in the two cohorts when stratified by multimorbidity level. Equal distributions of age, sex and index year showed that matching was done successfully. In the hip fracture cohort, 40% were categorized with no multimorbidity, 40% with moderate multimorbidity and 19% with severe multimorbidity. In the comparison cohort, 48% were categorized with no, 37% with moderate, and 15% with severe multimorbidity.

Further characteristics are provided in Table 1 and Table S3.

Infection Risk and Interaction Within 1 Month

The overall incidence rate within 1 month was 223.8 (220.1–227.5) per 100 person years in the hip fracture cohort, which is roughly 14 times higher than in the comparison cohort (Table 2). This matches the corresponding overall adjusted HR

Table 1 Characteristics of Hip Fracture Cohort and Comparison Cohort, Total and by Multimorbidity Level Defined by the Charlson Comorbidity Index

Characteristics, n(%)	Hip Fracture Cohort				Comparison Cohort			
	Multimorbidity Level							
	All	No	Moderate	Severe	All	No	Moderate	Severe
All	92,599 (100%)	37,345 (40%)	37,342 (40%)	17,912 (19%)	462,993 (100%)	222,419 (48%)	171,168 (37%)	69,406 (15%)
Sex								
Female	65,812 (71%)	28,696 (77%)	26,310 (70%)	10,806 (60%)	329,058 (71%)	161,241 (72%)	121,906 (71%)	45,911 (66%)
Male	26,787 (29%)	8,649 (23%)	11,032 (30%)	7,106 (40%)	133,935 (29%)	61,178 (28%)	49,262 (29%)	23,495 (34%)
Age in years								
65–75	20,737 (22%)	8,533 (23%)	7,753 (21%)	4,451 (25%)	104,106 (22%)	65,123 (29%)	29,519 (17%)	9,464 (14%)
76–85	37,672 (41%)	14,261 (38%)	15,493 (40%)	7,918 (44%)	188,605 (41%)	87,561 (39%)	70,653 (41%)	30,391 (44%)
86–95	31,246 (34%)	13,032 (35%)	12,972 (35%)	5,242 (29%)	155,932 (34%)	63,431 (29%)	65,028 (38%)	27,473 (40%)
>95	2,944 (3%)	1,519 (4%)	1,124 (3%)	301 (2%)	14,350 (3%)	6,304 (3%)	5,968 (3%)	2,078 (3%)
Index year								
2004–2008	31,674 (34%)	13,642 (37%)	12,733 (34%)	5,299 (30%)	158,370 (34%)	75,686 (34%)	59,904 (35%)	22,780 (33%)
2009–2013	31,702 (34%)	12,581 (34%)	12,886 (35%)	6,235 (35%)	158,510 (34%)	75,589 (34%)	58,791 (34%)	24,130 (35%)
2014–2018	29,223 (32%)	11,122 (30%)	11,723 (31%)	6,378 (36%)	146,113 (32%)	71,144 (32%)	52,473 (31%)	22,496 (32%)

Table 2 Crude and Standardized Incidence Rates for Hip Fracture Cohort and Comparison Cohort in Total and Stratified by Multimorbidity Level. Interaction Contrast and Proportion Attributed to Interaction for Moderate and Severe Multimorbidity. Adjusted Hazard Ratios

Multi-morbidity	Cohort	Events, N	Person Years	Crude Incidence Rates Per 100 Person Years (95% CI)	Standardized Incidence Rates Per 100 Person Years (95% CI)*	Interaction Contrast (95% CI)**	Attributed Proportion	Adjusted Hazard ratio (95% CI)***
1 month follow-up								
Total	Comparison	5755	37,649	15.3 (14.9–15.7)				Reference
	Hip fracture	14254	6370	223.8 (220.1–227.5)				14.2 (13.8–14.7)
No	Comparison	1492	1,817,453	8.2 (7.8–8.6)	8.8 (8.4–9.3)	Reference	Reference	Reference
	Hip fracture	4692	267,901	175.1 (170.2–180.2)	180.8 (175.6–186.2)			19.9 (18.8–21.1)
Moderate	Comparison	2445	1,389,760	17.6 (16.9–18.3)	16.9 (16.2–17.5)			Reference
	Hip fracture	6066	254,059	238.8 (232.8–244.8)	239.8 (233.8–245.9)	50.9 (42.8–59)	21.2	13.4 (12.8–14.0)
Severe	Comparison	1818	557,695	32.6 (31.1–34.1)	31.1 (29.7–32.7)			Reference
	Hip fracture	3496	114,992	304 (294.1–314.3)	301.9 (291.1–313.1)	98.8 (86.5–111.1)	32.7	9.1 (8.6–9.6)
1 year follow-up								
Total	Comparison	49584	410,594	12.1 (12.0–12.2)				Reference
	Hip fracture	25714	57,684	44.6 (44.0–45.1)				3.6 (3.6–3.7)
No	Comparison	14826	20,500,302	7.2 (7.1–7.3)	7.8 (7.6–7.9)	Reference	Reference	Reference
	Hip fracture	8206	2,636,952	31.1 (30.5–31.8)	32.9 (32.2–33.6)			4.0 (3.9–4.2)
Moderate	Comparison	21349	14,935,184	14.3 (14.1–14.5)	13.6 (13.4–13.8)			Reference
	Hip fracture	11020	2,248,032	49 (48.1–49.9)	50.1 (49.2–51.1)	11.4 (10.1–12.6)	22.7	3.4 (3.4–3.5)
Severe	Comparison	13409	5,623,936	23.8 (23.4–24.2)	22.7 (22.3–23.1)			Reference
	Hip fracture	6488	883,451	73.4 (71.7–75.2)	74.5 (71.1–78.0)	26.7 (23.1–30.2)	35.8	3.0 (2.9–3.1)

Notes: *Standardized by age in 5-year intervals, index year in 5-year intervals and sex in the total cohort. **Excess incidence rate attributed to interaction. ***Adjusted for age, sex, and index year.

of 14.2 (13.8–14.7) (Table 2). Incidence rates increased with multimorbidity level in both cohorts with the highest incidence rate found in the hip fracture cohort with severe multimorbidity. The interaction contrast was 50.9 (95% CI: 42.8–59) per 100 person years for hip fracture patients with moderate multimorbidity and 98.8 (86.5–111.1) for hip fracture patients with severe multimorbidity (Table 2, Figure 1).

HRs from the Cox regression that was used for calculation of interaction on relative scale are presented in Figure 2. HRs were substantially higher for the hip fracture sub-cohorts and increased with multimorbidity level. For instance, the HRs were 20 (95% CI: 19–21) and 34 (95% CI: 32–37) for hip fracture patients with no multimorbidity and severe multimorbidity, respectively, compared to the comparison cohort with no multimorbidity. The attributable fraction was 20.5% for hip fracture patients with moderate multimorbidity and 31.8% for hip fracture patients with severe multimorbidity (Figure 2).

Infection Risk and Interaction Within 1 Year

Within 1 year of follow-up, the incidence rates of infection were lower in the hip fracture cohort compared to 1-month of follow-up, whereas incidence rates in the comparison cohort did not change noticeably. The overall adjusted HR was 3.6 (3.6–3.7) for hip fracture patients compared to the comparison cohort (Table 2). The interaction contrast indicated that on absolute scale, 22.7% and 35.8% of incidence rates could be explained by interaction between hip fracture and moderate or severe multimorbidity.

https://doi.org/10.2147/CLEP.S507252

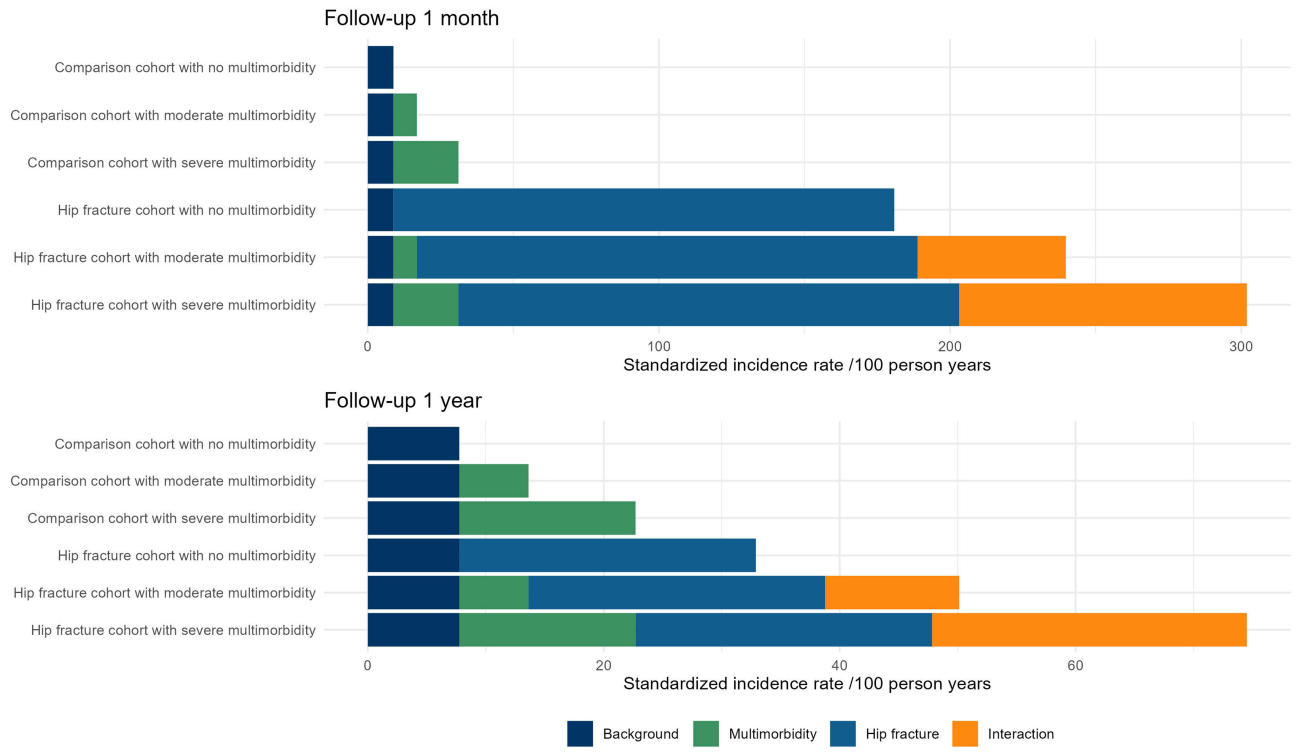

Figure 1 Interaction effect between Hip fracture surgery and multimorbidity on absolute scale based on stacked incidence rates.

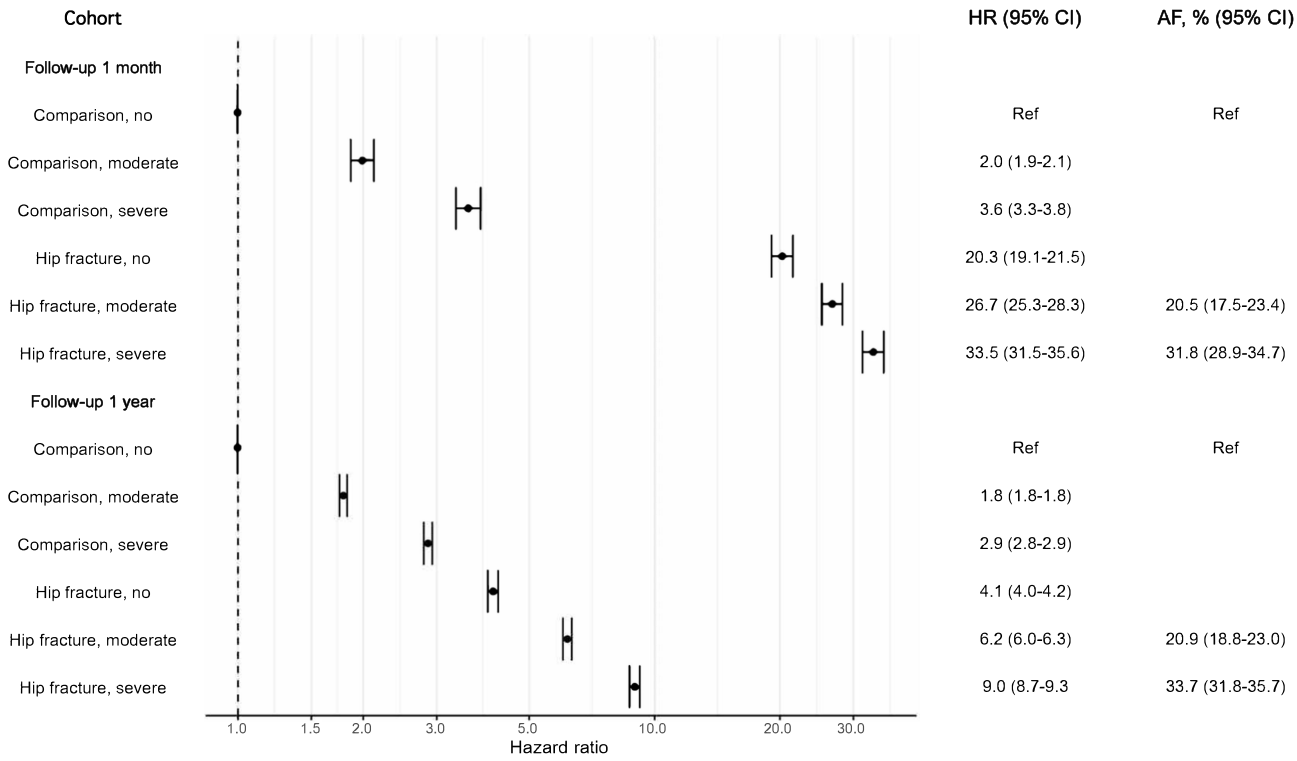

Figure 2 Adjusted hazard ratios (HR) for risk of infection comparing Hip fracture patients with no, moderate and severe multimorbidity, as well as comparison cohort with moderate and severe multimorbidity with the comparison cohort with no multimorbidity as a reference, and attributable fraction (AF).

https://doi.org/10.2147/CLEP.S507252

The attributable fraction indicated that on relative scale HRs could be reduced by 20.9% and 33.7% in hip fracture patients with moderate and severe multimorbidity if there was no interaction effect (Figure 2).

Discussion

We found that multimorbidity interacts with hip fracture surgery on both absolute and relative scale, increasing the risk of infection both within 1 month and 1 year after surgery. The interaction leads to 20–35% excess risk of post-surgical infection in hip fracture patients with multimorbidity.

Considerations With Respect to Existing Research

To our knowledge, no other studies have examined the interaction between multimorbidity and hip fracture surgery regarding infection risk. This is surprising since multimorbidity and infection are highly prevalent in hip fracture patients and an association between multimorbidity and elevated infection risk has been reported.[7] Previous interaction studies on hip fracture have focused on mortality and cardiovascular events.[11,12,13] A Norwegian study among female hip fracture patients found that in patients with a CCI score ≥3, 9 of 15 deaths per 100 patients could be attributed to interaction.[11] A Danish study investigated the interaction between previous stroke and hip fracture on mortality risk and found interaction on both absolute and relative scale within 30 days of follow-up and suggested that complications like infection might explain the excess mortality.[22] Two other studies investigated the interaction between comorbidity and hip fracture on the risk of cardiovascular events and found that interaction could explain up to 28% of excessive risk of venous thromboembolism and 76% of excessive risk of stroke and myocardial infarction.[12] Our study extends available knowledge by being the first to include a comparison cohort to investigate the association between multimorbidity and infection risk after hip fracture surgery and thereby finding excess risk due to interaction.

Potential Mechanisms and Clinical Implications

There are several potential explanations for the excess risk of infection in hip fracture patients with multimorbidity. Many factors are related to the hip fracture trauma and surgery itself. It is well known that intubation, catheterization, and opioid use can lead to infections like pneumonia and urinary tract infections. Also, dehydration, anemia, and post-operative immobilization can lead to higher risk of sustaining a post-surgical infection.[23–25] Some highly prevalent chronic diseases in hip fracture patients like chronic pulmonary disease lead to increased risk of infection due to deterioration in respiratory health, changes in lung function and both airway and systemic inflammation.[26] Some diseases included in the CCI are treated with immunomodulating drugs, which may also contribute to the infection risk.[27] Based on this, a possible explanation for the excess risk attributed to interaction is that multimorbidity amplifies the effect of factors related to hip fracture surgery that increase infection risk and vice versa.

It is highly relevant to prevent postoperative infections in hip fracture patients as infections are associated with high mortality.[8] First, focusing on primary prevention, including fall prevention and osteoporosis treatment, is essential.[3,28,29] Second, it is important to focus on early symptoms and detection of postoperative infections, as symptoms of infection in multimorbid patients might not be as typical as in patients without multimorbidity. Third, hip fracture patients with multimorbidity can benefit from an emphasis on the importance of early mobilization after surgery. Early mobilization and regaining baseline mobility before discharge has been found to be associated with a reduced risk of infection within 30 days but is less often achieved in patients with higher multimorbidity level.[25,30] Fourth, a Danish study found that involving of relatives in post-discharge home visits was associated with lower frequency of unplanned hospitalization within 30 days after discharge from acute disease for frail patients aged 65 years and above living alone. Therefore, it suggests that guidelines should also focus on structured involvement of relatives.[31] This could also be evident in post-discharge care of hip fracture patients and reduce risk of readmission due to infections.

Methodological Considerations

The positive predictive value (PPV) of hip fracture diagnosis and surgery in the Danish Multidisciplinary Hip Fracture Registry is 100%.[32] The completeness of the hip fracture registry is considered high, as reimbursement to orthopedic surgery departments is based on the registration of diagnosis and surgery codes. For the ICD-10 diagnosis codes used to define

multimorbidity, the PPV ranges from 82 to 100%.[18] Information on severity of individual diseases included in CCI was not available but severity was considered equally distributed between the hip fracture and comparison cohort. The prevalence of multimorbidity may be underestimated since only hospital-treated diseases were included. On the other hand, we also expect hospital-treated diseases to have the highest impact on infection risk. CCI was chosen over other indices as studies have found only little or no differences in predictive ability and CCI is widely used, making it easier to compare.[33]

A study conducted on cancer patients found that ICD-10 codes for any infection have a PPV of 98%.[34] We cannot exclude the risk of differential misclassification due to surveillance and detection bias if hip fracture patients are more likely to be admitted to the hospital. However, the risk is considered low as admission to hospital should be based on symptoms and paraclinical tests.

Our study could be biased by unmeasured confounding due to lifestyle factors such as smoking and BMI, and socioeconomic factors such as cohabitation and social network. However, some lifestyle factors such as mobility are more likely to be intermediate factors in the causal pathway than confounders.

Conclusion

There is an interaction effect between multimorbidity and hip fracture surgery on both absolute and relative scale that leads to a substantial elevated risk of infection. This effect increases with multimorbidity level. Targeted and personalized pre- and postoperative initiatives aimed at prevention, early detection of symptoms, and early treatment of infections should be considered among these vulnerable multimorbid hip fracture patients to a greater extend. We suggest that future clinical guidelines take multimorbidity into account.

Data Sharing Statement

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

Ethical Approval and Informed 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). By Danish law, patient consent is not required for research using routinely collected electronic health data.

Acknowledgments

The abstract of this paper was presented at the Danish Orthopedic Society (DOS) annual meeting as a conference talk with interim findings. The paper's abstract was published in DOS abstracts book 2024 in: [DOS Abstract Book 2024].

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by grants from the Independent Research Fund Denmark. The grant supporter had no influence on the data acquisition, analysis, interpretation, or reporting of the present study.

Disclosure

CMH reports personal fees from Sygehus Lillebælt Orthopedic Department, outside the submitted work. NRG, CMVG and ABP are salaried employees as Aarhus University or Aarhus University Hospital. The Department of Clinical Epidemiology, Aarhus University, receives funding for other studies from companies in the form of research grants to and administered by Aarhus University. None of these studies have any relation to the present study. NPH reports contracts or grants from Swedish Research Council, Stiftelsen Promobilia, Skobranschens utvecklingsfond, and

Waldemar Link and has affiliations with the Swedish National Board of Health and Welfare, Swedish Arthroplasty Register, Nordic Association of Arthroplasty Registers, and Biobank Sweden. No contracts, grants or affiliations reported by NPH present any conflict or have any relation to the present study. He also reports personal fees from DePuy Johnson Johnson, Warsaw, Indiana, USA, personal fees from Zimmer Biomet, Winterthur, Switzerland, personal fees from Heraeus Medical, Wehrheim, Germany, outside the submitted work. The authors report no other conflicts of interest in this work.

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