Clinical Epidemiology

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ORIGINAL RESEARCH

Delay in surgery, risk of hospital-treated infections and the prognostic impact of comorbidity in hip fracture patients. A Danish nationwide cohort study, 2005–2016

This article was published in the following Dove Press journal:
Clinical Epidemiology

Eva N Glassou[1,2]
Kaja KE Kjørholt[3]
Torben B Hansen[1]
Alma B Pedersen[3]

[1]University clinic for hand, hip and knee surgery, Regional Hospital West Jutland, Aarhus University, Holstebro 7500, Denmark; [2]Department of Quality, Regional Hospital West Jutland, Holstebro 7500, Denmark; [3]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N 8200, Denmark

Purpose: We examined the association between delay in surgery and hospital-treated infections in hip fracture patients with and without known comorbidities.

Patients and methods: All hip fracture patients aged ≥65 years registered in the Danish Multidisciplinary Hip Fracture Registry from 2005 to 2016 were included (n=72,520). Delay in surgery was defined as the time in hours from admission to surgery and was divided into 3 groups (12, 24 and 48 hrs). The outcomes were hospital-treated pneumonia, urinary tract infection and reoperation due to infection 0–30 days after surgery. As a measure of comorbidity, we used the Charlson Comorbidity Index (CCI): none (no registered comorbidities prior to the fracture), medium (1–2 points) and high (≥3 points).

Results: Overall, there was an association between a delay of 12 hrs and pneumonia. A delay of 12 hrs was associated with an increased risk of pneumonia in patients with no comorbidities (adjusted hazard ratio (HR) 1.20, confidence interval (CI) 1.03–1.40) and a delay of 24 hrs was associated with an increased risk of pneumonia in patients with a medium level of comorbidity (HR 1.12, CI (1.02–1.23)). Overall, delay was associated with reoperation due to infection, particularly among patients with comorbidities, although the confidence intervals of some of the estimates were wide. A delay of 48 hrs was associated with an increased risk of reoperation due to infection in patients with a high level of comorbidity (HR 2.36, CI 1.19–4.69).

Conclusion: Delay in surgery was associated with an increased risk of hospital-treated pneumonia and reoperations due to infection within 30 days of surgery. The number of postoperative hospital-treated infections within 30 days may be reduced by continuously targeting pre-, per- and postoperative optimization not only for patients with high level of comorbidity but also for hip fracture patients without known comorbidities prior to surgery.

Keywords: hip fracture, delay in surgery, pneumonia, urinary tract infection, reoperation, surgical site infection

Introduction

Hip fractures, with an annual incidence rate in Denmark of approximately 4.2 per 1,000 person-years, are a leading cause of hospital admissions, disability and increased mortality risk in the elderly population.[1] The typical hip fracture patient is often frail, elderly and multicomorbid; is in polypharmacy treatment; has underlying cognitive discords; and is dehydrated due to a significant time lapse from trauma to admission.[2]

Correspondence: Eva N Glassou
Department of Quality, Regional Hospital West Jutland, Lægårdvej 12, Holstebro DK-7500, Denmark
Tel +457 843 8706
Email evagla@rm.dk

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DovePress
http://doi.org/10.2147/CLEP.S200454

Therefore, these patients are vulnerable to both trauma and subsequent surgery, as well to the potential complications that may occur in relation to surgery and immobilization.

In addition to the patients' own medical state, a delay in surgery may be associated with an increased risk of complications such as pressure wounds, urinary tract infections (UTIs), pneumonia and mortality.[3–11] However, a delay in surgery may be favorable in some hip fracture patients, allowing time for a beneficial stabilization of the patient's medical condition and a proper discontinuation of anticoagulant drugs, commonly used in this patient group.[4]

The recommendation from the National Institute for Health and Care Excellence is surgery on the day of admission, or the day after.[12] Additionally, studies have shown that 24 hrs may represent a threshold in relation to mortality and complications.[13] In Denmark, the national guidelines recommend that at least 75% of hip fracture patients receive surgery within 24 hrs,[14] but this recommendation has recently become an object of debate. To reduce the mortality risk, which is associated with a delay in surgery, several argue for a further reduction in the delay in surgery. As hip fracture patients compete with other surgery patients for a limited amount of resources at the hospital, including clinical staff and operation rooms, better risk stratification of this patient group is needed. A potential association between delay in surgery and risk of infections may, in this context, be of importance. Therefore, our aim was to examine how delay in surgery affects the risk of an infection in hip fracture patients with and without known comorbidities.

Materials and methods

Study population

Through the Danish Multidisciplinary Hip Fracture Registry (DMHFR) we included all first-time hip fracture patients 65 years or older who underwent primary hip replacement or open reduction and internal fixation between January 1, 2005, and December 31, 2016 (n=74,791). In total, 2,271 patients were excluded due to either missing follow-up (20 patients), missing information about delay (170 patients) or delay of more than 75 hrs (2,081 patients), which we interpreted as a result of registration errors. In total, 72,520 patients met the inclusion criteria and were included in the final analyses.

Data sources

Based on each resident's unique 10-digit personal identification number encoding age, sex and date of birth, data were collected from four databases and linked to a final dataset on an individual level.

The DMHFR is a nationwide clinical quality database holding individual data on all patients ≥65 years old with femoral neck, per-trochanteric or sub-trochanteric fractures treated surgically since 2003 (see appendix 1 for codes according to the International Classification of Diseases (ICD), revision 10). Reporting in the DMHFR is mandatory, and data are collected prospectively during hospital admission using standardized registration forms in the electronic patient records.[15,16] Detailed definitions of data elements are provided to ensure uniform registration of data across departments. Due to the registration method, the completeness is >95%.[14] The DMHFR was used to identify the study population and obtain information about fracture type, time of hospitalization and surgery (and by that delay in surgery), type of surgery, body mass index (BMI) and marital status.

The Danish Civil Registration System was initiated in 1968 and contains records of all Danish residents, among other records of residence and date of death. The CRS is updated daily.[17] The Danish Civil Registration System provided information about the date of death.

The Danish National Patient Register contains information on surgical procedures and primary discharge diagnoses and up to 20 secondary discharge diagnoses on all inpatient admissions and outpatient visits to Danish hospitals.[18] Diagnoses are coded according to the ICD. The Danish National Patient Register provided information about infections during the index hospitalization or readmission. Additionally, the register provided information about comorbidities at the time of surgery and 10 years prior to surgery, based on the ICD codes.

The Danish National Health Service Prescription Database contains complete data on all reimbursed prescriptions dispensed from community pharmacies and hospital-based outpatient pharmacies in Denmark since 2004.[19] The drugs are coded according to the Anatomical Therapeutic Chemical classification system. The database provided information about drug use prior to the hip fracture.

Exposure - delay in surgery

Delay in surgery was defined as time in hours from the hospital admission to the start of surgery. Patients are classified as those with delays in surgery within 12 hrs, 24 hrs or 48 hrs. We compared patients with and without delay within 12 hrs, as well as patients with and without delay within 24 hrs and 48 hrs. This approach is taken to

reduce the potential for unmeasured confounding. Thus, prolonged waiting time for surgery may indicate medical rather than administrative reasons for delay and may introduce confounding factors. In addition, the time of admission during the day may be considered a confounder. Further, with this comparison, we can potentially define the threshold for delayed surgery in relation to infection risk.

Outcome - hospital treated infection

The outcome was the presence of any of the following 3 conditions: hospital-treated UTI, hospital-treated pneumonia and reoperation due to infection, all 3 between 0 (day of surgery) and 30 days after surgery. For all 3 infections, the first hospital-treated infection during either the index hospitalization or a re-admission or an outpatient clinic visit at a private or a public hospital forms the basis of the analyses. The follow-up period of 0–30 days was chosen to represent the early postoperative period and the first period after discharge. This period represents a clinically important and, from the patients' point of view, a vulnerable period where the health-related effect of hip surgery may be maintained or lost.

Covariates

We measured the following covariates as of the surgery date: age (in categories; 65–74, 75–79, 80–84, 85–90 and 90+ years), sex, BMI (in categories; underweight: BMI <18.5 kg/m^2, normal weight: BMI ≤18.5–24.9 kg/m^2, overweight: BMI 25.0–29.9 kg/m^2 and obese: BMI ≥30.0 kg/m^2), comorbidity level, marital status (married, not married), type of fracture (femoral neck and sub-/pertrochanteric fractures), type of surgery (osteosynthesis and hemi/total arthroplasty) and surgery year (biannual). Furthermore, we included the use of corticosteroids, anti-osteoporotic medicine, non-steroidal anti-inflammatory drugs, oral anticoagulants, statins, selective serotonin reuptake inhibitors and antibiotics due to the potential association between these drugs and infection risk. Patients were categorized into nonusers (no redemption of a prescribed specific drug in the year prior to surgery), former users (redemption of at least one prescription drug 91–365 days prior to hip fracture surgery) and current users (at least one prescription drug ≤90 days prior to hip fracture surgery).

The comorbidity level was measured with the Charlson Comorbidity Index (CCI) score. We defined three comorbidity levels; none, given to patients with no previous record of diseases included in the CCI; a medium level of comorbidity and a high level of comorbidity, given to patients with a record of diseases equaling CCI-index scores at 1 to 2 and 3 or more, respectively. All primary and secondary diagnoses included in the CCI (see appendix 1 for ICD, revision 10 codes) and registered in relation to hospitalizations and outpatient visits over a ten-year period before the hip fracture formed the basis of the CCI calculation. In addition to the CCI, we included the presence of an alcoholism-related disease as an individual comorbid condition.

All relevant ATC codes and ICD codes used to define the study population, infections and comorbidities are available in appendix 1. The distribution of diseases from the Charlson index according to delay in surgery is also available in appendix 1.

Statistics

Patient characteristics were tabulated as proportions by delay in surgery. We calculated the incidence rates (IRs) per 1,000 person-years with 95% confidence intervals (CIs) for each of the 3 infections. Using the Cox proportional hazards regression model censoring at death, we calculated crude and adjusted hazard ratios (HRs) with corresponding 95% CIs to evaluate the impact of delay in surgery on the risk of infections within 0–30 days. HRs were adjusted for age, sex, comorbidity level, type of fracture and year of surgery. The impact of delay in surgery on the risk of infections was examined by stratifying for comorbidity level, leaving this covariate out of the adjustment. The proportional hazards assumptions were controlled graphically and by log-minus log plot, and found to be fulfilled.

All statistical analyses were performed using STATA Version 15.0 (Stata Corp LP, College Station, TX, USA).

Ethics

The study was approved by the Danish Data Protection Agency (Region of Central Denmark journal number 1–16-02–444-15).

Results

Patient characteristics according to delay in surgery are presented in Table 1. Patients who were delayed more than 24 or 48 hrs were slightly more comorbid, sustained a femoral neck fracture, were treated with a hemi- and total arthroplasty and were current users of oral anticoagulation. The absolute difference in the proportion

Table 1 Patient characteristics according to delay of surgery

	Delay >12 hrs				Delay >24 hrs				Delay >48 hrs			
	No, ≤12		Yes, >12		No, ≤24		Yes, >24		No, ≤48		Yes, >48	
Total	**N 14,616**	**% 20**	**N 57,904**	**% 80**	**N 45,152**	**% 62**	**N 27,368**	**% 38**	**N 67,291**	**% 93**	**N 5,229**	**% 7**
Patient-related variables												
Sex												
Female	10,394	71	41,450	72	32,482	72	19,362	71	48,226	72	3,618	69
Male	4,222	29	16,454	28	12,670	28	8,006	29	19,065	28	1,611	31
Age, in years												
65–74	2,918	20	10,988	19	8,827	20	5,079	19	12,940	19	966	18
74–79	2,329	16	9,442	16	7,224	16	4,547	17	10,828	16	943	18
80–84	3,114	21	12,920	22	9,824	22	6,210	23	14,867	22	1,167	22
85–89	3,347	23	13,633	24	10,441	23	6,539	24	15,741	23	1,239	24
90+	2,908	20	10,921	19	8,836	620	4,993	18	12,915	19	914	17
Body Mass Index												
<18.5	1,290	9	4,970	8	3,967	9	2,293	8	5,854	9	406	8
≥18.5–24.9	6,693	46	26,335	45	20,704	46	12,324	45	30,764	46	2,264	43
≥25.0–29.9	2,804	19	11,471	20	9,008	20	5,267	19	13,209	20	1,066	20
≥30	779	5	3,221	6	2,472	5	1,528	6	3,709	5	291	6
Unknown	3,050	21	11,907	21	9,001	20	5,956	22	13,755	20	1,202	23
Charlson Comorbidity Index												
Low (0)	6,016	41	23,301	40	18,730	41	10,587	39	27,395	41	1,922	37
Medium (1–2)	5,787	40	23,550	41	18,056	40	11,281	41	27,110	40	2,227	42
High (3+)	2,813	19	11,053	19	8,366	19	5,500	20	12,786	19	1,080	21
Alcohol-related disease												
None	14,079	96	55,897	79	43,574	97	26,402	96	64,899	96	5,077	97
1 or more	537	4	2,007	3	1,578	3	966	4	2,392	4	152	3
Marital status												
Unmarried	10,196	70	40,959	71	31,842	71	19,313	71	47,506	71	3,649	70
Married	4,420	30	16,945	29	13,310	29	8,055	29	19,785	29	1,580	30
Fracture-related variables												
Type of fracture												
Femoral neck	7,272	50	30,947	53	23,202	51	15,017	55	35,209	52	3,010	58
Per-/subtrochanter	7,344	50	26,957	47	21,950	49	12,351	45	32,082	48	2,219	42
Type of surgery												
Osteosynthesis	11,185	76	39,038	67	32,399	72	17,824	65	47,085	70	3,138	60
Hemi/total Arthroplasty	3,431	24	18,866	33	12,753	28	9,544	35	20,206	30	2,091	40
Year of surgery												
2005–2006	2,363	16	9,528	16	6,772	15	5,119	19	10,785	16	1,106	21
2007–2008	2,342	16	10,346	18	7,189	16	5,499	20	11,558	17	1,130	22

(*Continued*)

Table 1 (Continued).

	Delay >12 hrs				Delay >24 hrs				Delay >48 hrs			
	No, ≤12		Yes, >12		No, ≤24		Yes, >24		No, ≤48		Yes, >48	
Total	**N 14,616**	**% 20**	**N 57,904**	**% 80**	**N 45,152**	**% 62**	**N 27,368**	**% 38**	**N 67,291**	**% 93**	**N 5,229**	**% 7**
2009–2010	2,178	15	10,136	18	7,239	16	5,075	19	11,263	17	1,051	20
2011–2012	2,516	17	9,849	17	7,886	18	4,479	16	11,567	17	798	15
2013–2014	2,652	18	9,435	16	8,312	18	3,775	14	11,479	17	608	12
2015–2016	2,565	18	8,610	15	7,754	17	3,421	12	10,639	16	536	10
Medication use before surgery												
Corticosteriods												
Non-users	13,054	89	51,919	90	40,548	90	24,425	89	60,322	90	4,651	89
Former users	615	4	2,485	4	1,888	4	1,212	4	2,875	4	225	4
Current users	947	7	3,500	6	2,716	6	1,731	6	4,094	6	353	7
Anti-osteoporotic medication												
Non-users	13,046	89	52,216	90	40,553	90	24,709	90	60,501	90	4,761	91
Former users	393	3	1,492	3	1,223	3	662	3	1,764	3	121	2
Current users	1,177	8	4,196	7	3,376	7	1,997	7	5,026	7	347	7
Non-Steroidal Anti-Inflammatory Drugs												
Non-users	11,499	79	45,197	78	35,461	79	21,235	78	52,646	78	4,050	77
Former users	1,479	10	6,002	10	4,633	10	2,848	10	6,928	10	553	11
Current users	1,638	11	6,705	12	5,058	11	3,285	12	7,717	12	626	12
Oral anti-coagulants												
Non-users	7,933	54	29,546	51	24,288	54	13,191	48	35,146	52	2,333	45
Former users	1,403	10	5,719	10	4,287	9	2,835	10	6,538	10	584	11
Current users	5,280	36	22,639	39	16,577	37	11,342	42	25,607	38	2,312	44
Statins												
Non-users	11,120	76	43,767	76	34,191	76	20,696	76	50,955	76	3,932	75
Former users	873	6	3,674	6	2,772	6	1,775	6	4,186	6	361	7
Current users	2,623	18	10,463	18	8,189	18	4,897	18	12,150	18	936	18
Selective Serotonin Reuptake Inhibitors												
Non-users	11,095	76	44,351	77	34,446	76	21,000	77	51,448	76	3,998	76
Former users	608	4	2,321	4	1,865	4	1,064	4	2,727	4	202	4
Current users	2,913	20	11,232	19	8,841	20	5,304	19	13,116	20	1,029	20
Antibiotics												
Non-users	7,554	52	30,521	53	23,664	52	14,411	53	35,296	53	2,779	53
Former users	3,487	24	13,972	24	10,807	24	6,652	24	16,220	24	1,239	24
Current users	3,575	24	13,411	23	10,681	24	6,305	23	15,775	23	1,211	

of these variables was less than 4%. In general, the proportion of patients with a delay of more than 24 hrs decreased during 2005–2016 with a turning point between 2010 and 2011. The presence of specific comorbidities at the time of surgery was not associated with surgery delay. Of the 19 disease topics included in the

CCI, only congestive heart failure and cerebrovascular disease had a small impact on the delay in surgery. We observed only slightly (2–3%) more patients with congestive heart disease and cerebrovascular disease in patients with a delay in surgery of more than 24 hrs or 48 hrs compared to 12 hrs (Appendix 1).

Hospital treated infections

In total, 7,287 (10%) of the patients experienced a hospital-treated infection within 0–30 days after surgery. UTI accounted for 4,205 (45%) of all infections, pneumonia accounted for 3,805 (41%) and reoperations due to infection accounted for 253 (3%). The number of infections, incidence rates and hazard ratios for the hospital-treated infections are presented in Table 2.

Delay in surgery was associated with hospital-treated pneumonia. Overall, a delay of >24 hrs resulted in an increased risk of hospital-treated pneumonia (HR 1.09, CI: 1.02–1.16). A similar association was observed between a delay of >24 hrs and patients with a medium comorbidity burden (HR 1.12, CI: 1.02–1.23). In addition, delays of >12 hrs and >24 hrs were associated with a HR of 1.20 (CI: 1.03–1.40) and a HR of 1.11 (CI: 0.98–1.26) for hospital-treated pneumonia in patients with no previous comorbidity.

Overall, a delay of more than 12 hrs was associated with an increased risk of reoperation due to infection within 30 days (HR 1.41, CI: 1.00–1.99). In addition, a delay of 48 hrs was associated with an increased risk of reoperation due to infection within 30 days (HR 1.51, CI: 1.01–2.26). Stratification on comorbidity suggests that delays of 12 hrs, 24 hrs and 48 hrs among patients with moderate and high comorbidity burden were associated with an increased risk of reoperation. However, due to the small sample size and number of outcomes, these estimates should be interpreted with caution.

UTI was the most frequent hospital-treated infection. The incidence rate was approximately 2.1 per 1,000 person-years regardless of delay in surgery. We found no associations between delay and UTI, either overall or in regard to the comorbidity burden.

Discussion

Delay in surgery was associated with an increased risk of hospital-treated pneumonia and reoperations due to infection. A delay of only 12 hrs increased the risk of pneumonia in patients with no known comorbidity prior to surgery. For patients with a medium level of comorbidity, a delay of 24 hrs increased the risk of pneumonia and for patients with a high level of comorbidity, a delay of 48 hrs increased the risk of reoperation due to infection.

The best design when evaluating the effect of delay in surgery would be a randomized controlled trial. However, this is not possible due to ethical and practical reasons, and a large cohort study with the advantages of prospectively and independently collected data is the second best design. This study is, to the best of our knowledge, the largest cohort study evaluating the effect of delay in surgery on the risk of specific hospital-treated infections.

A comparison of studies is in general difficult due to a great variability in both delay cut-offs and the definitions of postoperative complications. Delay cut-offs of more than 24 hrs are not comparable with Danish conditions as more than 60% of patients are treated within 24 hrs. Additionally, an outcome of only early in-hospital complications is not applicable, as we leave out the infections causing readmissions. Nevertheless, both Simunovic et al and Klestil et al concluded in their reviews that early surgery is associated with fewer peri- and postoperative complications including pneumonia.[6,10] These findings are supported by Pincus et al who, in a large cohort study from Canada, showed that increased delay in surgery (>24 hrs) was associated with an increased risk of postoperative complications (within 30 days of surgery) including pneumonia.[13] As both the exposure and the outcome in Pincus et al are comparable to those in our study, our results add further evidence to the association between early surgery and reduced risk of postoperative pneumonia.

In relation to UTI, our findings support the general impression that delay in surgery does not affect the risk of early postoperative UTI.[20–22] Smektala et al found no effect of delay on the risk of UTI in a prospective cohort study of 2,916 hip fracture patients from Germany.[22] Similar findings were made by Majumdar et al in a Canadian retrospective cohort study. Here, they found that a delay of 24 or 48 hrs had no effect on the risk of in-hospital UTI.[21]

We found that the association between delay of surgery and risk of postoperative pneumonia was most distinct for patients with no known comorbidities or a medium level of comorbidities at the time of the hip fracture. This is not intuitive and not identical to earlier findings. Klestil et al suggest in a recent review that patients with comorbidities often benefit from surgery within 24 hrs.[10] Since patients with a number of comorbidities prior to the hip fracture are more susceptible to

Table 2 Incidence rate and hazard ratios (HR with 95% confidence interval (CI) for the 3 specific hospital-treated infections within 0–30 days following hip fracture surgery. HRs were adjusted for age, sex, comorbidity burden (CCI), type of fracture and year of surgery. When stratifying for comorbidity, the CCI-variable was left out of the analysis

0-30 days						
	In total Number of UTI	Incidence per 1000 person years (ci)	All	Stratified CCI low	CCI medium	CCI high
			HR (ci)	HR (ci)	HR (ci)	HR (ci)
≤12 hours	830	2.11 (1.97 – 2.26)	1.00	1.00	1.00	1.00
>12 hours	3,375	2.16 (2.09 – 2.24)	1.03 (0.95 – 1.11)	1.06 (0.93 – 1.20)	1.00 (0.89 – 1.13)	1.03 (0.87 – 1.21)
≤24 hours	2,597	2.13 (2.05 – 2.21)	1.00	1.00	1.00	1.00
>24 hours	1,608	2.19 (2.09 – 2.30)	1.03 (0.97 – 1.10)	1.07 (0.96 – 1.18)	1.00 (0.91 – 1.10)	1.03 (0.90 – 1.17)
≤48 hours	3,915	2.16 (2.09 – 2.23))	1.00	1.00	1.00	1.00
>48 hours	290	2.06 (1.83 – 2.31)	0.96 (0.85 – 1.08)	1.04 (0.85 – 1.27)	0.95 (0.79 – 1.14)	0.89 (0.69 – 1.14)
0-30 days						
	In total Number of pneumonia	Incidence per 1000 person years (ci)	All	Stratified CCI low	CCI medium	CCI high
			HR (ci)	HR (ci)	HR (ci)	HR (ci)
≤12 hours	754	1.90 (1.77 – 2.04)	1.00	1.00	1.00	1.00
>12 hours	3,051	1.93 (1.87 – 2.00)	1.04 (0.96 – 1.12)	1.20 (1.03 – 1.40)	0.92 (0.82 – 1.04)	1.09 (0.93 – 1.27)
≤24 hours	2,315	1.88 (1.80 – 1.95)	1.00	1.00	1.00	1.00
>24 hours	1,490	2.01 (1.91 – 2.12)	1.09 (1.02 – 1.16)	1.11 (0.98 – 1.26)	1.12 (1.02 – 1.23)	1.02 (0.90 – 1.15)
≤48 hours	3,528	1.93 (1.86 – 1.99)	1.00	1.00	1.00	1.00
>48 hours	277	1.95 (1.73 – 2.19)	1.03 (0.91 – 1.17)	1.06 (0.84 – 1.35)	1.00 (0.83 – 1.20)	1.05 (0.84 – 1.32)
0-30 days						
	In total Number of reoperations due to infection	Incidence per 1000 person years (ci)	All	Stratified CCI low	CCI medium	CCI high
			HR (ci)	HR (ci)	HR (ci)	HR (ci)
≤12 hours	38	0.09 (0.07 – 0.13)	1.00	1.00	1.00	1.00
>12 hours	215	0.13 (0.12 – 0.15)	1.41 (1.00 – 1.99)	1.48 (0.84 – 2.60)	1.25 (0.73 – 2.14)	1.59 (0.76 – 3.36)
≤24 hours	148	0.12 (0.10 – 0.14)	1.00	1.00	1.00	1.00
>24 hours	105	0.14 (0.11 – 0.17)	1.17 (0.91 – 1.50)	0.87 (0.57 – 1.34)	1.38 (0.92 – 2.05)	1.35 (0.81 – 2.25)
≤48 hours	226	0.12 (0.11 – 0.14)	1.00	1.00	1.00	1.00
>48 hours	27	0.18 (0.13 – 0.27)	1.51 (1.01 – 2.26)	0.93 (0.41 – 2.14)	1.53 (0.82 – 2.88)	2.36 (1.19 – 4.69)

Abbreviations: DMHFR, Danish Multidisciplinary Hip Fracture Registry; h, hours; CCI, Charlson Comorbidity Index, HR, hazard ratio; CI, confidence interval; UTI, urinary tract infection; BMI, body mass index; NSAIDs, Non Steroidal Anti-Inflammatory Drugs (NSAIDs); SSRI, Selective Serotonin Reuptake Inhibitor.; ICD, International Classification of Diseases revision 10.

a longer hospital stay than are patients without known comorbidity prior to the hip fracture, it is possible that registration of hospital-treated infections during the index hospitalization is more likely underestimated among high vs low comorbidity patients. However, any underestimation of infection registration during index hospitalization, as well as any underestimation of infection during the follow-up period, will most likely be nondifferential, thus independent of the delay in surgery. On the other hand, if hip fracture in less comorbid patients is the first apparent proof of a medical deterioration, then the findings about an association between surgery delay and risk of infection in less comorbid patients is not that surprising. Here, further studies are needed.

As mentioned, the international recommendations regarding surgery after hip fracture are surgery on the day of admission, or the day after.[12] Additionally, 24 hrs may represent a threshold defining complications.[13] According to Kelly-Pettersson et al, there is no safe time frame, and additionally, the risk of serious adverse events may increase for every 10 hrs of delay of surgery.[9] In view of this and our results, it seems reasonable to assume that the number of hospital-treated infections within 30 days can be reduced if one complies with the guidelines or even better ensures surgery within 12 hrs.

Limitations

Delay in surgery may be due to several reasons. Organizational reasons may delay surgery. This affects patients with femoral neck fractures and therefore patients in need of hemi- or total arthroplasties as these surgeries demand skilled surgeons who are not always on duty. Additionally, the patient's medical condition may call for a physiological optimization after the fracture, thus delaying surgery. This affects patients with a high comorbidity burden and with current use of oral anti-coagulation. Hypothetically, poor use of the delay in the less vulnerable patients, compared to that in patients with a known high comorbidity level at the time of surgery, could lead to an association between delay in surgery and hospital-treated pneumonia in the less vulnerable patients. Unfortunately, we have no information about why surgery is delayed (medical or organizational reasons) and if the time is well spent. Therefore, we cannot rule out residual confounding. Inclusion of both pathological and nonpathological fractures may have biased our estimates. However, patients with longer surgery delays were not more likely to have a diagnosis of "any tumor" and "metastatic tumor" than patients with shorter surgery delays (Appendix 1). Therefore, we do not believe this would have had a strong impact on our findings. Additionally, we have no exact knowledge about how many patients with a high energy trauma hip fracture were included in our study population, but we expect it to be minimal.

Stratification for comorbidity burden is made with the CCI. The index has been developed to summarize complex medical histories, offering statistical efficiency and straightforward interpretation compared with the inclusion of individual comorbid diseases in statistical models or stratified analyses. The index is frequently used in studies based on register data. The limitation of the index is that it precludes the estimation of the effects of individual comorbid diseases. However, stratifying on the CCI rather than specific comorbid diseases provides an overall and crude effect of delay on infection risk in comorbid and healthy patients. Since the index does not take the severity of a disease into account, residual confounding may still be present. Additionally, since the CCI does not capture diseases treated only by general practitioners, we might have underestimated the number of hip fracture patients with a comorbidity burden. We lacked measurements of frailty and nutrition status, as well as other lifestyle factors, and socioeconomic factors that have previously been reported as risk factors for infection. These factors could also be related to surgery delay.

Conclusion

Delay in surgery was associated with an increased risk of hospital-treated pneumonia and reoperations due to infection. Delays in surgery of 12 hrs and 24 hrs increased the risk of hospital-treated pneumonia in patients with no known and medium levels of comorbidity prior to surgery. A delay of 48 hrs increased the risk of reoperation due to infection in patients with a high level of comorbidity prior to surgery.

However, the association was modest, and one can argue that time from hospitalization to surgery is used for beneficial stabilization of the patient's medical condition. When held against the current national and international guidelines, the number of hospital-treated infections within 30 days may, however, be reduced if delay in surgery is shortened. Additionally, an increased focus on the less comorbid patients seems beneficial. These patients may, in fact, be patients with a hip fracture as the first apparent proof of a medical deterioration. To balance confounding, further studies looking at the association between delay of surgery and infection need to be conducted with prospective registration of the reason for the delay.

Disclosure

The authors report no conflicts of interest in this work.

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Appendix 1

Any hospital-treated (inpatient or outpatient) infections, collected from The Danish National Patient Register.

Infection	ICD revision 10 diagnose codes
Miscellaneous bacterial infections	A20-A38, A42-A44, A48-A49, A65-A79
Bacteremia	A49.9, A39.4
Sepsis	A40-A41,A32.7, A54.86, A02.1, A22.7, A26.7, A42.7, A28.2B
Abscess	A54.1,, D73.3, E06.0A, E23.6A, E32.1, G06, G07, H00.0A, H05.0A, H44.0A, H60.0, J34.0A, J36, J38.3D, J38.7G, J39.0, J39.1, J39.8A, J85.1, J85.2, J85.3, K04.6, K04.7, K11.3, K12.2, K13.0A, K14.0A, K20.9A, K35.3A, K35.3B, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K75.0, K81.0A, K85.8A, L02, L05.0, L05.9, M60.8A, M86.8A, M86.9A, N15.1, N34.0, N41.2, N45.0, N48.2, N49.2A, N61.9A, N61.9B, N70.0A, N70.0B, N71.0A, N73.0A, N73.0B, N73.2A, N73.2B, N73.3A, N73.5A, N73.8A, N73.8C, N75.1, N76.4, N76.8A, Except: A54.1B, B43.0, B43.8, B43.9, K57.0B, K57.0C, K57.2B, K57.2C, K57.4A, K65.0M, K65.0N, K65.0O, K65.0P
Skin infections	A46, H01.0, H03, H60.0, H60.1, H60.2, H60.3, H62, K12.2, K13.0, K61, M72.6, L01, L08.0, L08.1,
Cellulitis	L03
Other skin infections	J34.0, L00, L02, L04, L05, L06, L07, L30.3, L73.8
Eye infections	H00, H01.0, H03.0, H03.1, H04.3, H05.0, H06.1, H10, H13.0, H13.1, H15.0, H19.1, H19.2, H22.0, H32.0, H44.0, H44.1
Ear infections	H60, H61.0, H62.0, H62.1, H62.2, H62.3, H65, H66, H67.0, H67.1, H68, H70, H73.0, H75.0, H83.0, H94.0 Except: H60.4, H60.4A, H605, H60.5B, H60.8, H608.A, H65.2, H65.3, H65.4, H65.4C, H66.1, H66.2, H66.3, H68.1, H70.1, H70.8
Central Nervous System infections	G00-07 (except meningococcal disease)
Meningitis	G00, G01, G02, G03, A32.1, A39.0, A17.0, A20.3, A54.8D, A02.2C
Gastrointestinal infections:	A00, A01, A02, A03, A04, A05, A09
Intra-abdominal infection	K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0, K85.9
Heart infections (acute rheumatic fever, infectious pericarditis or myocarditis, endocarditis):	I00-I02, I30.1, I32.0, I33, I38, I40.0, I39.8, B37.6
Upper respiratory tract infection	J00-J06, J36, J39.0, J39.1
Pneumonia	J12, J13, J14, J15, J16.0, J17, J18
Other lower-respiratory tract infections:	J20-J22, J44.0, J85.1, J86, J20-J22, J34.0, J35.0, J38.3C, J38.3D, J38.7B, J38.7F, J38.7G Except: J34.0E, J34.0F, J34.0G, J34.0H
Urinary tract infections	N10, N11, N12, N15.1, N15.9, N30, N33.0, N34, N39.0, N08.0, N13.6, N16.0, N28.8D, N28.8E, N28.8F, N29.0, N29.1 Except: N30.1, N30.2, N30.4
Sexually transmitted diseases	A50-A64
Male genital infections	N41, N45, N48.1, N48.2, N49, N51.1, N51.2
Female pelvic infections	N70-77
Septic arthritis, osteomyelitis, myositis	M00, M01, M86, M63.0, M63.2
Infectious complications of procedures, catheters etc.	T80.2, T81.4, T82.6, T82.7, T83.5, T83.6, T84.5, T84.6, T84.7, T85.7, T88.0, T89.9
Other infections or sequelae	B90-B99, K04.0, K05.2
Reoperation due to infection	**ICD revision 10 diagnose codes**
Procedures	
NFW69: Do not require combination with ICD-10 codes but can be combined with ICD-10 code	T84.5, T84.6, T84.7
NFS 0-99: In combination with ICD-10 code	
NFU 0-99: In combination with ICD-10 code	

(*Continued*)

(Continued).

NFC20-99: If NFB is primary operation type, in combination with ICD-10 code	
Diagnoses included in Charlton comorbidity index **Disease**	**ICD revision 10 diagnose codes**
Myocardial infarction	I21;I22;I23
Congestive heart failure	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	I60-I69; G45; G46
Dementia	F00-F03; F05.1; G30
Chronic pulmonary disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	M05; M06; M08; M09;M30;M31;M32; M33; M34; M35; M36; D86
Ulcer disease	K22.1; K25-K28
Mild liver disease	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes, type1 and type2	E10.0, E10.1; E10.9; E11.0; E11.1; E11.9
Hemiplegia	G81; G82
Moderate to severe renal disease	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end organ damage	E10.2-E10.8; E11.2-E11.8
Any tumor	C00-C75
Leukemia	C91-C95
Lymphoma	C81-C85; C88; C90; C96
Moderate to severe liver disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	C76-C80
AIDS	B21-B24
Alcoholism-related disease **Disease**	**ICD revision 10 diagnose codes**
Alcohol related disorder	F10
Alcohol induced chronic pancreatitis	K86.0
Finding of alcohol in blood	R78.0
Toxic effect of alcohol	T51
Alcoholic gastritis without bleeding	K29.2
Alcoholic polyneuropathy	G62.1
Alcoholic myopathy	G72.1
Degeneration of nervous system due to alcohol	G31.2
Alcoholic cardiomyopathy	I42.6
Drug use prior to the hip fracture **Drug**	**Anatomical Therapeutic Chemical classification system - ATC-codes**
Systemically absorbed glucocorticoids	H02BX
Statins	C10AA01, C10AA02, C10AA03 C10AA04, C10AA05, C10AA06,
Anti-osteoporosis medicine Anti-osteoporosis medicine	M05BA01, B05BB01, M05BA02, M05BA03, M05BA04, M05BB03, M05BB05, M05BA06, M05BA07, M05BB02, M05BB04, M05BX04, M05BX03, G03XC01, H05AA02
Non-steroidal Anti-Inflammatory Drugs	M01AH01, M01AH, M01AH03, M01AH05, M01AC05, M01AB05, M01ACO6, M0A1
Oral anti-coagulants	B01AB, B01AX, A01AD, B01AA, B01AE07, B01AF01, B01AF02, B01AF03, B01AC, N02BA01, N02BA51
Selective Serotonin Reuptake Inhibitors	N06AB03, N0GAB04, N06AB05, N06AB06, N06AB08, N06AB10
Antibiotics	J01X, J05X

The distribution of diseases from the Charlson index according to delay in surgery. All primary and secondary diagnoses included in the CCI and registered in relation to hospitalizations and outpatient visits over a ten-year period before the hip fracture form the basis for having (yes) og not having (no) a specific comorbid disease at the time of surgery.

	Delay > 12 hours				**Delay >24 hours**				**Delay >48 hours**			
	No, ≤12		**Yes, >12**		**No, ≤24**		**Yes, >24**		**No, ≤48**		**Yes, >48**	
Myocardial infarction												
Yes	804	5	3,140	5	2,360	5	1,584	6	3,610	5	334	6
No	13,812	95	54,764	95	42,792	95	25,784	94	63,681	95	4,895	94
Congestive heart failure												
Yes	1,227	8	5,382	9	3,712	8	2,897	11	5,970	9	639	12
No	13,389	92	52,522	91	41,440	92	24,471	89	61,321	91	4,590	88
Peripheral vascular disease												
Yes	1,145	8	4,575	8	3,426	8	2,294	8	5,259	8	461	9
No	13,471	92	53,329	92	41,726	92	25,074	92	62,032	92	4,768	91
Cerebrovascular disease												
Yes	2,558	18	10,732	19	8,010	18	5,280	19	12,201	18	1,089	21
No	12,058	82	47,172	81	37,142	82	22,088	81	55,090	82	4,140	79
Dementia												
Yes	1,433	10	5,611	10	4,381	10	2,663	10	6,566	10	478	9
No	13,183	90	52,293	90	40,771	90	24,705	90	60,725	90	4,751	91
Chronic pulmonary disease												
Yes	1,756	12	7,261	13	5,411	12	3,606	13	8,344	12	673	13
No	12,860	88	50,643	87	39,741	88	23,762	87	58,947	88	4,556	87
Connective tissue disease												
Yes	666	5	2,754	5	2,087	5	1,333	5	3,146	5	274	5
No	13,950	95	55,150	95	43,065	95	26,035	95	64,145	95	4,955	95
Ulcer disease												
Yes	837	6	3,271	6	2,512	6	1,596	6	3,771	6	337	6
No	13,779	94	54,633	94	42,640	94	25,772	94	63,520	94	4,892	94
Mild liver disease												
Yes	162	1	635	1	478	1	319	1	738	1	59	1
No	14,454	99	57,269	99	44,674	99	27,049	99	66,553	99	5,170	99
Diabetes I and II												
Yes	1,181	8	4,975	9	3,783	8	2,373	9	5,697	8	459	9
No	13,435	92	52,929	91	41,369	92	24,995	91	61,594	92	4,770	91
Hemiplegia												
Yes	35	0	147	0	102	0	80	0	165	0	17	0
No	14,581	100	57,757	100	45,050	100	27,288	100	67,126	100	5,212	100
Moderate to severe renal disease												

(*Continued*)

(Continued).

	Delay > 12 hours				Delay >24 hours				Delay >48 hours			
	No, ≤12		Yes, >12		No, ≤24		Yes, >24		No, ≤48		Yes, >48	
Yes No	545 14,071	4 96	2,166 55,738	4 96	1,626 43,526	4 96	1,085 26,283	4 96	2,484 64,807	4 96	227 5,002	4 96
Diabetes with end organ damage												
Yes No	649 13,967	4 96	2,845 55,059	5 95	2,127 43,025	5 95	1,367 26,001	5 95	3,197 64,094	5 95	297 4,932	6 94
Any tumor												
Yes No	2,234 12,382	15 85	8,344 49,560	14 86	6,590 38,560	15 85	3,988 23,380	15 85	9,824 57,467	15 85	754 4,475	14 86
Leukemia												
Yes No	72 14,544	0 100	283 57,621	0 100	215 44,937	0 100	140 27,228	1 99	329 66,962	0 100	26 5,203	0 100
Lymphoma												
Yes No	123 14,493	1 99	489 57,415	1 99	371 44,781	1 99	241 27,127	1 99	571 66,720	1 99	41 5,188	1 99
Moderate to severe liver disease												
Yes No	74 14,542	1 99	231 57,673	0 100	198 44,963	0 100	116 27,252	0 100	277 67,014	0 100	28 5,201	1 99
Metastatic solid tumor												
Yes No	290 14,326	2 98	801 57,103	1 99	688 44,464	2 98	403 26,965	1 99	1,005 66286	1 99	86 5,143	2 98
AIDS												
Yes No	3 14,613	0 100	13 57,981	0 100	9 45,143	0 100	7 27,361	0 100	15 67,276	0 100	1 5,228	0 100