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Impact of comorbidity on the association between surgery delay and mortality in hip fracture patients: A Danish nationwide cohort study

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ABSTRACT

Purpose: To examine the association between surgery delay and mortality in hip fracture patients with and without known comorbidity.
Methods: We identified all patients with a first time hip fracture diagnose operated between January 1, 2010 and December 31, 2015 (n = 36,552). As a measure of comorbidity we used Charlson Comorbidity Index stratified in categories: none (no registered comorbidities prior fracture), medium (1–2 points) and high (≥3 points).
Results: No association between surgery delay, regardless of the threshold, and 30-days mortality was observed among patients with high level of comorbidity. Surgery delay of >24h vs. ≤24 h was associated with higher 0–30-days mortality in patients with medium level of comorbidity (adjusted HR: 1.12 (95% CI: 1.01 ; 1.24)). In addition, surgery delay was associated with up to 45% increased mortality in patients with none comorbidity prior surgery, although the confidence intervals were wide. Furthermore, surgery delay of >24 h (vs. <24 h) and >48 h (vs. ≤48 h) was associated with higher 31–90-days mortality among all patients (adjusted HR: 1.19 (95% CI: 1.10 ; 1.29) and 1.35 (95% CI: 1.16 ; 1.56), respectively), but in particular among patients with none (adjusted HR: 1.26 (95% CI: 1.08 ; 1.47) and 1.65 (95% CI: 1.26 ; 2.17), respectively) and medium (adjusted HR: 1.21 (95% CI: 1.07 ; 1.36) and 1.25 (95% CI: 1.00 ; 1.57), respectively) level of comorbidity at the time of surgery.
Conclusions: There was an association between surgery delay and 30-days mortality in hip fracture surgery patients with none and medium level of comorbidity, whereas no such association was observed among hip fracture patients with a high comorbidity level. Surgery delay was associated with one year increased risk of dying in both patients with and without comorbidity prior surgery.

Introduction

Mortality following hip fracture is very high. A meta-analysis, based on studies from 1957 to 2009 showed that the all-cause mortality in the first 3 months after hip fracture incidence was 6-fold in women and 8-fold in men compared with the general population [1]. Overall mortality within one year following hip fracture is more than 30%, but highly dependent on the comorbidity level before hip fracture [2].

A systematic review from 2010 showed that surgery delay was associated with mortality up to one year after surgery [3]. The optimal timing of surgery is a long-standing controversy and a frequent clinical concern in the acute management of patients with hip fracture [4]. Proponents of early treatment argue that this approach minimizes the length of time a patient is confined to bed rest, thereby reducing the risk for associated complications, such as pressure sores, deep vein thrombosis, and urinary tract infections. Those favoring delaying surgery beyond the guideline recommendations believe that this approach is required to medically optimize patients, and therefore decrease the risk for perioperative complications [5]. The lack of a broadly accepted threshold for surgery delay illustrates that the controversy remains. Previous studies have used different thresholds for surgery delay, i.e., 12 [6,7], 24 [6,8] and 48 h [6] without clear

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guideline for clinical indication. Furthermore, there is a paucity of available data on the impact of comorbidity on the association between surgical delay and subsequent mortality [7]. Only five out of the 16 studies included in the systematic review presented adjusted estimates of mortality [3], most commonly adjusted for American Anesthetists Society score (a measure of a patient's fitness for surgery), age and sex. The role of comorbidity prior surgery, measured with the presence of different medical conditions, on the association between surgery delay and mortality has so far not been examined in details, although it is likely to be important [2]. It may be hypothesized that time delays are less critical in hip fracture patients with comorbidities as the delay can be used to ensure preoperative optimization. In contrast, time delays may be more critical among hip fracture patients without known comorbidity prior admission, who may less likely to be offered preoperative optimization as they are considered to be "healthy" patients. Hence, we aimed to determine whether the association between surgery delay and mortality differ between hip fracture patients with and without known comorbidities. If increasing surgery delay is associated with increasing mortality both in patients with and without comorbidity, this would be an argument for further strengthening the efforts to minimize surgery delay in all patients.

Thus, the aim of this study was to examine the association between surgery delay and mortality in hip fracture patients with and without comorbidities at the time of surgery.

Methods

Study design and setting

This study was a nationwide cohort study using prospective collected data from Danish administrative and medical registers. The Danish National Health Service provides tax-supported health care for the entire Danish population [9].

Data sources

Patients were identified in the Danish Multidisciplinary Hip Fracture Database (DMHFD) which is a nationwide population-based clinical quality database established in 2003. The database includes patients older than 65 years of age with a primary diagnosis of hip fracture and a hip fracture operation in the same hospitalization [10]. The DMHFD contains detailed clinical data related to hip fracture treatment and quality of in-hospital care indicators.

We used data from the Danish National Patient Registry (DNPR), which is a population-based administrative registry. This database holds data from all Danish hospitals since 1977 with complete nationwide coverage since 1978. Information reported to DNPR includes administrative data, diagnoses, treatments and examinations related to hospitalizations, outpatient and emergency room visits and data are updated continuously. Until 1993

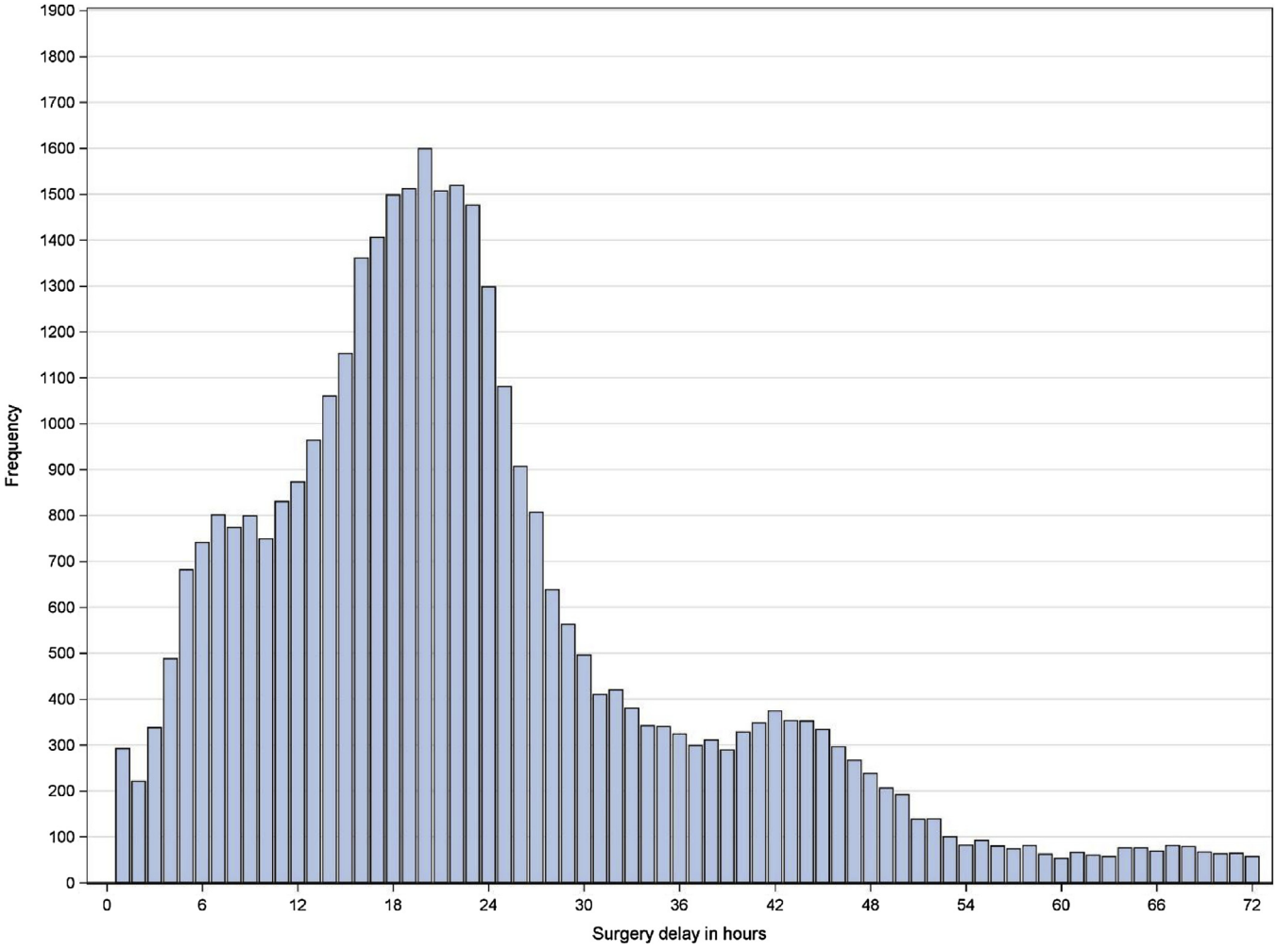

Fig. 1. Distribution of surgery delay among patients.

diagnoses were classified according to the International Classification of Diseases, Revision 8 (ICD-8) and the ICD-10 thereafter [9].

Further, The Danish Civil Registration System (CRS) was used. CRS is also an administrative register in Denmark established on April 2, 1968, and contains individual-level information on all persons residing in Denmark and daily updated information on migration and vital status [11].

Finally, data from The Danish National Database of Reimbursed Prescriptions (DNDRP) was used. DNDRP contains the reimbursement records of all reimbursed drugs sold in community pharmacies and hospital-based outpatient pharmacies in Denmark since 2004 and covers the entire Danish population including residents of long-term care institutions. DNDRP contains variables such as pharmaceutical form, trade name, Anatomical Therapeutic Chemical (ATC) Classification System code, and Defined Daily Dose (DDD) of the medicinal product [12].

Data from the different data sources were linked together using the Civil Personal Registration (CPR) number, which is a unique 10-digit personal identification number. This number is the key component of register linkage in Denmark, as it is used in all Danish administrative and medical registers [11].

Study population

We identified all patients with a first time hip fracture diagnose operated between January 1, 2010 and December 31, 2015 (n = 37,532). Patients with surgery delay of more than 72 h were excluded as there was most likely an error in the registration of either the time of admission or surgery. A total of 36,552 patients were included in the final study population.

Surgery delay

Surgery delay was defined as the time (in hours) from hospital admission to surgery. We defined five dichotomous variables: i) delay more than 3 h ii) delay more than 6 h iii) delay more than 12 h iv) delay more than 24 h and v) delay more than 48 h.

Mortality

As outcome, 0–30-days and 31–90-days all-cause mortality was investigated. 0–30-days all-cause mortality was defined as death within 30 days after surgery and 31–90-days all-cause mortality as death within 90 days after surgery among patients who were alive at day 31 after surgery. As supplementary analysis, 91–180-days and 181–365-days all-cause mortality was also assessed.

Covariates

From the DMHFD following variables were included: sex, age (65–74, 75–84, 85+ years), body mass index (BMI) (underweight: 0–18.5, normal: 18.5–25, overweight: 25+ kg/m^2 when categorized according to the World Health Organisation [13]), type of fracture (fracture of femoral neck, per-/sub-trochanter fractures), type of

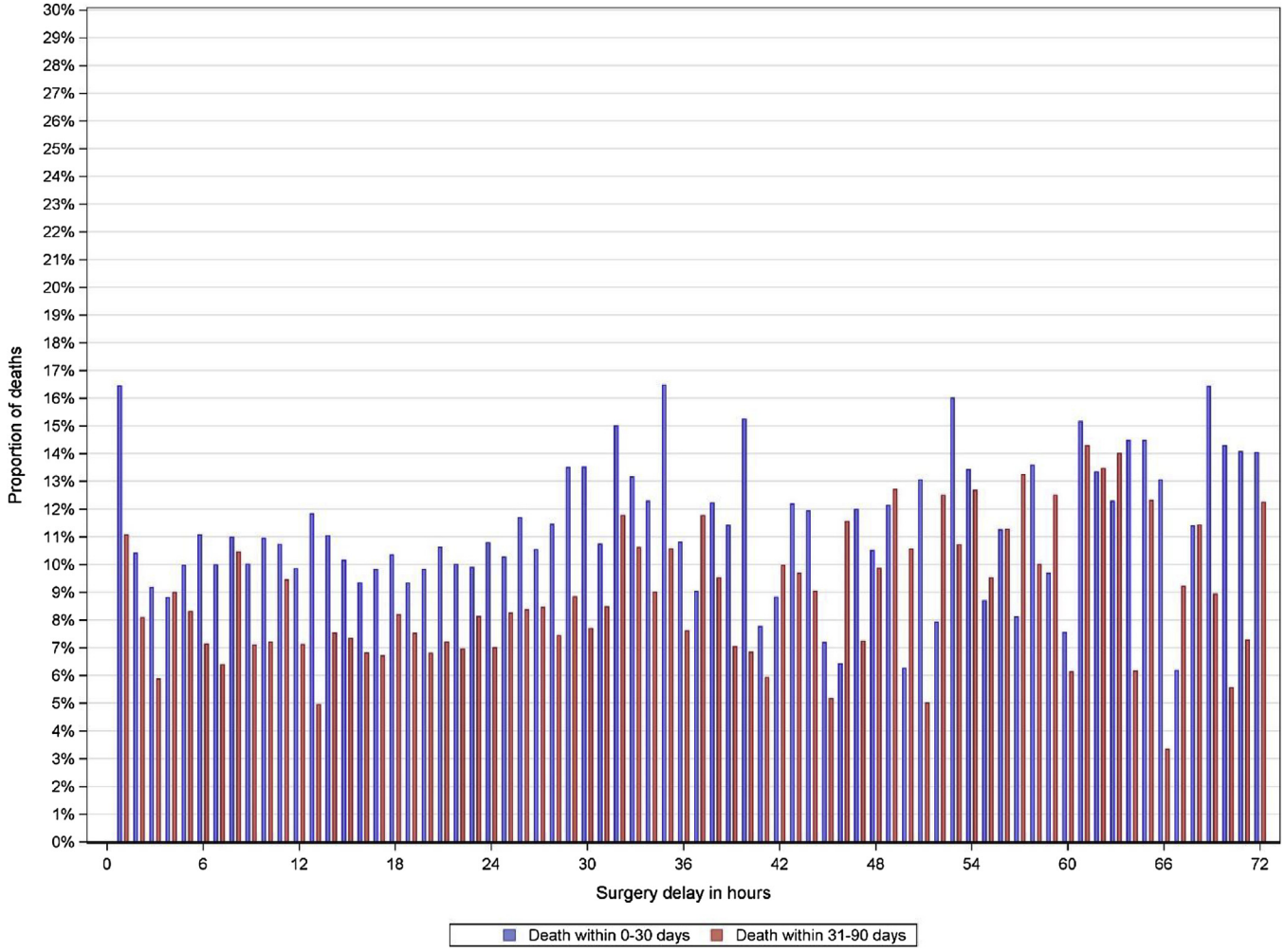

Fig. 2. Proportion of deaths within 0–30-days and within 31–90-days.

surgery (osteosynthesis, total/hemi hip arthroplasty), housing condition (care center, own home) and marital status (not married, married). In addition, comorbidity history was included measured by Charlson Comorbidity Index (CCI) (none: 0 point, medium: 1–2 points, high: >2 points) from the DNPR. Charlson Comorbidity Index is an approach to classify patients with comorbid diseases according to their risk of death from those diseases at the time of enrollment into the study. The index contains 19 disease categories each assigned score 1–6 according to strength of association with one year mortality. It is a weighted index that takes into account the number and for many diseases also the seriousness of the comorbid diseases [14]. Furthermore, information about use of anticoagulation drugs, psychiatric drugs, NSAIDs and steroids (non-users and users) were included from the DNDRP. Users of drugs were defined as patients with at least one date of redemption ≤365 days before surgery and non-users of drugs were patients with no prescription within 365 days before hip fracture surgery.

All codes used in the study is provided in the electronic Supplementary material, Table 1.

Statistics

We tabulated characteristics of the study population by calculating proportions. Bivariate analysis of the explanatory variables against the outcome was performed to identify the variables to be used in the multivariable model. To evaluate the association between surgery delay and mortality, crude and adjusted Hazard Ratios (HRs) were calculated using Cox proportional hazards

Table 1
Patient characteristics according to surgery delay.

	Delay > 12 h				Delay > 24 h				Delay > 48 h				Total	
	No		Yes		No		Yes		No		Yes			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	7588	100	28964	100	23941	100	12611	100	34438	100	2114	100	36552	100
Gender														
Female	5327	70.2	20491	70.7	17061	71.3	8757	69.4	24386	70.8	1432	67.7	25818	70.6
Male	2261	29.8	8473	29.3	6880	28.7	3854	30.6	10052	29.2	682	32.3	10734	29.4
Age category														
65–74	1616	21.3	5761	19.9	4917	20.5	2460	19.5	6946	20.2	431	20.4	7377	20.2
75–84	2692	35.5	10698	36.9	8615	36.0	4775	37.9	12579	36.5	811	38.4	13390	36.6
85+	3280	43.2	12505	43.2	10409	43.5	5376	42.6	14913	43.3	872	41.2	15785	43.2
BMI category														
No data	1334	17.6	5213	18.0	4034	16.8	2513	19.9	6093	17.7	454	21.5	6547	17.9
Underweight (BMI < 18.5)	666	8.78	2450	8.46	2109	8.81	1007	7.99	2964	8.61	152	7.19	3116	8.52
Normal (18.5 < =BMI<25)	3595	47.4	13309	46.0	11208	46.8	5696	45.2	15986	46.4	918	43.4	16904	46.2
Overweight(25 < =BMI<30)	1993	26.3	7992	27.6	6590	27.5	3395	26.9	9395	27.3	590	27.9	9985	27.3
CCI category														
None (0)	3026	39.9	11395	39.3	9688	40.5	4733	37.5	13676	39.7	745	35.2	14421	39.5
Medium (1–2)	3007	39.6	11714	40.4	9578	40.0	5143	40.8	13824	40.1	897	42.4	14721	40.3
High (3+)	1555	20.5	5855	20.2	4675	19.5	2735	21.7	6938	20.1	472	22.3	7410	20.3
Type of fracture														
Fracture of femoral neck	3856	50.8	15764	54.4	12534	52.4	7086	56.2	18374	53.4	1246	58.9	19620	53.7
Per and sub-trochanter fractures	3732	49.2	13200	45.6	11407	47.6	5525	43.8	16064	46.6	868	41.1	16932	46.3
Type of surgery														
Osteosyntheses	5609	73.9	18609	64.2	16460	68.8	7758	61.5	23035	66.9	1183	56.0	24218	66.3
Total and hemi hip arthroplasty	1979	26.1	10355	35.8	7481	31.2	4853	38.5	11403	33.1	931	44.0	12334	33.7
Housing condition														
No data	773	10.2	3337	11.5	2447	10.2	1663	13.2	3799	11.0	311	14.7	4110	11.2
Care center	1361	17.9	4768	16.5	4049	16.9	2080	16.5	5827	16.9	302	14.3	6129	16.8
Own home	5454	71.9	20859	72.0	17445	72.9	8868	70.3	24812	72.0	1501	71.0	26313	72.0
Marital status														
Not married	5187	68.4	20294	70.1	16678	69.7	8803	69.8	24016	69.7	1465	69.3	25481	69.7
Married	2401	31.6	8670	29.9	7263	30.3	3808	30.2	10422	30.3	649	30.7	11071	30.3
Anticoagulation drugs														
Non-users	4836	63.7	17433	60.2	15054	62.9	7215	57.2	21138	61.4	1131	53.5	22269	60.9
Users	2752	36.3	11531	39.8	8887	37.1	5396	42.8	13300	38.6	983	46.5	14283	39.1
Psychiatric drugs														
Non-users	5214	68.7	20364	70.3	16724	69.9	8854	70.2	24089	69.9	1489	70.4	25578	70.0
Users	2374	31.3	8600	29.7	7217	30.1	3757	29.8	10349	30.1	625	29.6	10974	30.0
NSAIDs														
Non-users	6870	90.5	26146	90.3	21660	90.5	11356	90.0	31122	90.4	1894	89.6	33016	90.3
Users	718	9.46	2818	9.73	2281	9.53	1255	9.95	3316	9.63	220	10.4	3536	9.67
Steroids														
Non-users	7132	94.0	27287	94.2	22584	94.3	11835	93.8	32450	94.2	1969	93.1	34419	94.2
Users	456	6.01	1677	5.79	1357	5.67	776	6.15	1988	5.77	145	6.86	2133	5.84

regression models. The HRs were adjusted for age, gender, BMI, type of fracture, type of surgery, housing condition, marital status, CCI, use of anticoagulation drugs, psychiatric drugs, NSAIDs and steroids, and calculated overall and stratified on CCI. Further, we stratified on specific diseases included in the CCI. The assumption of proportional hazards in the dataset were controlled visually by plotting log (cum hazard) as a function of follow up time and found to be appropriate [15]. All statistical analyses was performed with using of SAS 9.4 statistical software (SAS Institute Inc., Cary, USA).

Ethical approval

Study was approved by the Danish Data Protection Agency (journal number 1-16-02-467-15).

Results

Population characteristics

The distribution of surgery delay among the patients is shown in Fig. 1. A total of 7588 (20.76%) patients had a delay of maximum 12 h, 23,941 (65.50%) had a delay of maximum 24 h and 34,438 (94.22%) had a delay of maximum 48 h. Fig. 1 shows that the majority of patients had a delay between 18–24 hours. Fig. 2 shows the proportion of deaths within 0–30-days and within 31–90-days. We observed some variation in mortality in relation to surgery delay, without any clear association.

Patient characteristics according to surgery delay are shown in Table 1. Comparing characteristics of the patients with surgery delay ≤24 versus >24 h, we saw that the distribution of gender, age, BMI, housing condition and marital status was similar in these two groups. Compared to patients with surgery delay ≤24 h, patients with surgery delay >24 h were slightly more comorbid, had more fractures of femoral neck, total and hemi arthroplasty procedures, and more patients had received anticoagulation drugs. Similar findings regarding fracture type and surgery type were observed for patients with surgery delay >12 versus ≤12 h and those with surgery delay >48 versus ≤48 h.

Descriptive statistics on patients with surgery delay more than 3 h vs less than 3 h and more than 6 h vs less than 6 h are shown in the electronic Supplementary material, Table 2.

0–30-days mortality

The absolute mortality risk and corresponding adjusted HRs with 95% CIs are presented in Fig. 3. Overall absolute mortality risks were between 10.3% and 12.0% depending on the surgery delay. The adjusted HR for 0-30-days mortality varied from 0.87 (95% CI: 0.72 ; 1.06) for patients with surgery delay over 3 h compared with patients with delay less than 3 h to 1.07 (95% CI: 1.00 ; 1.14) for patients having more than 24 h surgery delay compared with patients with surgery delay ≤24 h. Thus, we observed no clear threshold for surgery delay indicating increased mortality when looking into entire study population.

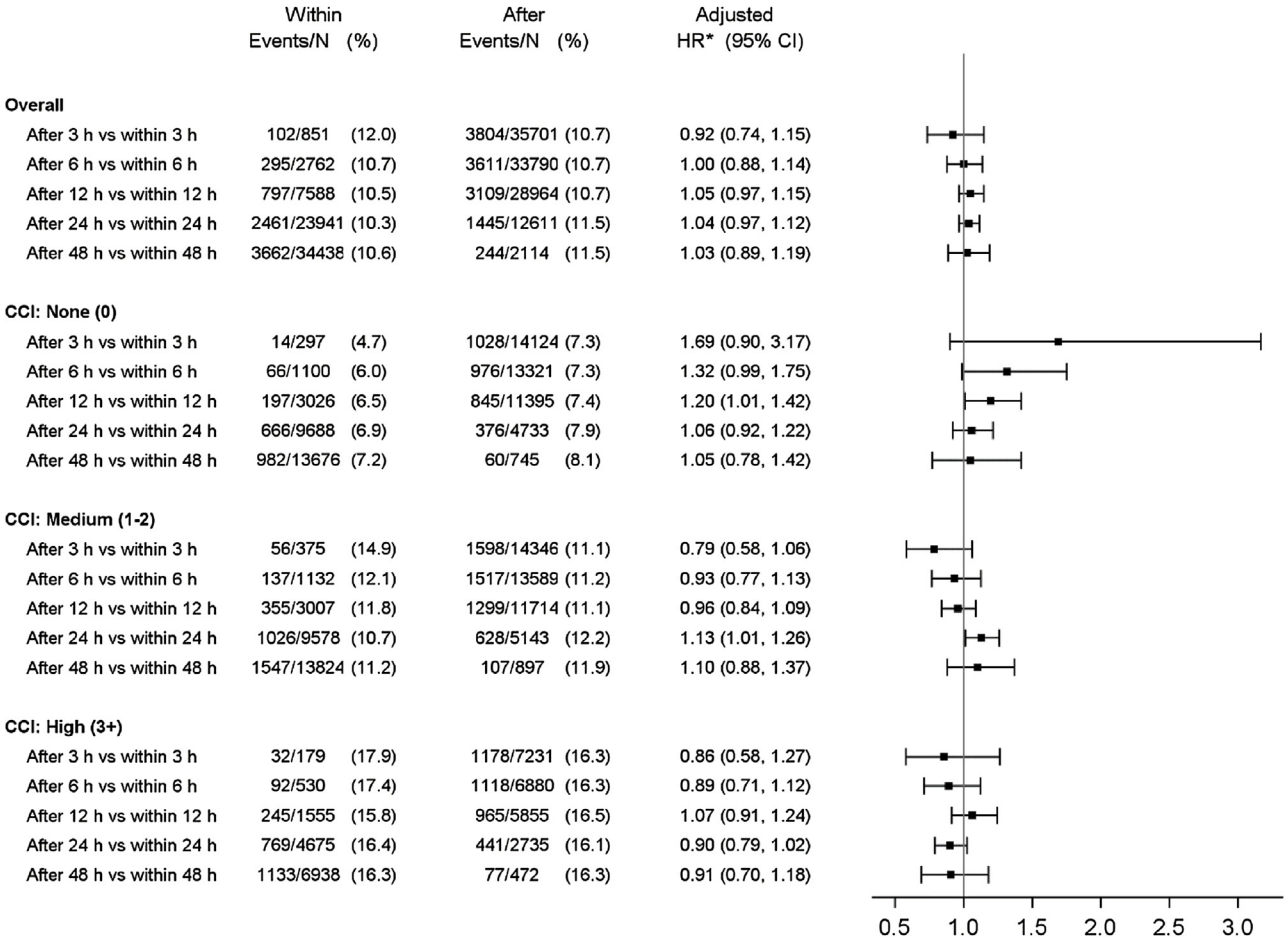

Fig. 3. 0–30-days mortality.
* Adjusted for age, gender, BMI, type of fracture, type of surgery, housing condition, marital status, CCI, use of anticoagulation drugs, psychiatric drugs, NSAIDs and steroids.

The analysis stratified by comorbidity showed that the absolute mortality risks increased with increasing comorbidity level irrespective of surgery delay. Our stratified analyses suggest no association between surgery delay and mortality among hip fracture patients with high comorbidity. However, patients with a medium level of comorbidity having more than 24 h surgery delay had increased 0–30-days mortality compared with patients having less than 24 h surgery delay (adjusted HR: 1.12 (95% CI: 1.01 ; 1.24)). In addition, our stratified analyses suggest that surgery delay might be associated with an increased mortality in patients with none comorbidity prior surgery, although the confidence intervals were wide.

31–90-days mortality

Overall absolute mortality risks 31–90-days after surgery were between 7.4% and 8.1% depending on the surgery delay (Fig. 4). In the overall analysis, patients having more than 24 h surgery delay had an increased adjusted HR of death within 31–90-days of 1.19 (95% CI: 1.10 ; 1.29) compared with patients having ≤24 h surgery delay. Furthermore, patients with a surgery delay of more than 48 h had an adjusted HR for death of 1.35 (95% CI: 1.16 ; 1.56) compared with patients with surgery delay of less than 48 h.

Similar associations for the thresholds of 24 and 48 h were observed among patients with none and medium comorbidity level. Thus, there were increased adjusted HRs when patients had more than 24 or 48 h delay, for patients with none comorbidity prior surgery (adjusted HR: 1.26 (95% CI: 1.08 ; 1.47) and 1.65 (95% CI: 1.26 ; 2.17), respectively) and for patients with medium level of comorbidity (adjusted HR: 1.21 (95% CI: 1.07 ; 1.36) and 1.25 (95% CI: 1.00 ; 1.57) respectively). In addition, there was an association between surgery delay and mortality for patients with high level of comorbidity (adjusted HR: 1.10 (95% CI: 0.95 ; 1.28)) in patients with surgery delay >24 vs. ≤ 24 h and 1.21 (95% CI: 0.91 ; 1.59) in patients with surgery delay >48 vs. ≤ 48 h), although the confidence intervals were wide.

91–180-days and 181–365-days mortality

In the electronic Supplementary material, Figs. 1 and 2 the analysis investigating 91–180-days and 181–365-days overall and stratified mortality are shown. The results are mainly in consistent with the result for 31–90-days mortality.

Surgery delay and mortality according to specific comorbidities

The association between surgery delay and mortality stratified on various disease groups was examined for the threshold of 24 h (Fig. 5). We observed no association between surgery delay and 30-days mortality for patients with individual comorbidities prior surgery. Surgery delay >24 vs ≤24 h was associated with increased 30-days mortality among patients having ulcer disease (adjusted HR: 1.44 (95% CI: 1.12 ; 1.86). When 31–90-days mortality was examined, a significant difference between the two groups was present for CPD and renal disease. Patients with CPD having a surgery delay more than 24 h had an adjusted HR of 1.26 (95% CI 1.04 ; 1.54) for 31–90-days mortality than patients with a surgery

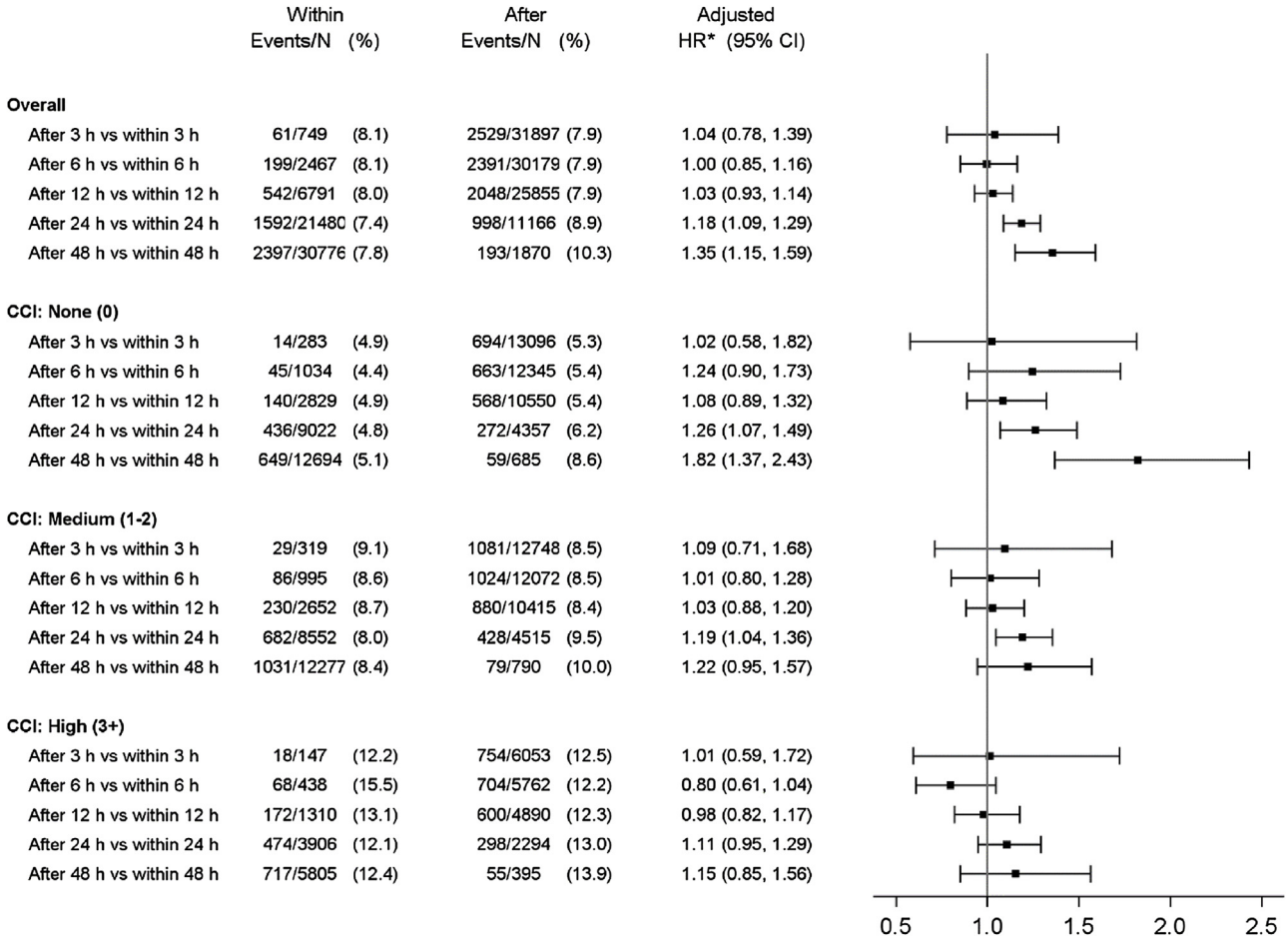

Fig. 4. 31–90-days mortality.
* Adjusted for age, gender, BMI, type of fracture, type of surgery, housing condition, marital status, CCI, use of anticoagulation drugs, psychiatric drugs, NSAIDs and steroids.

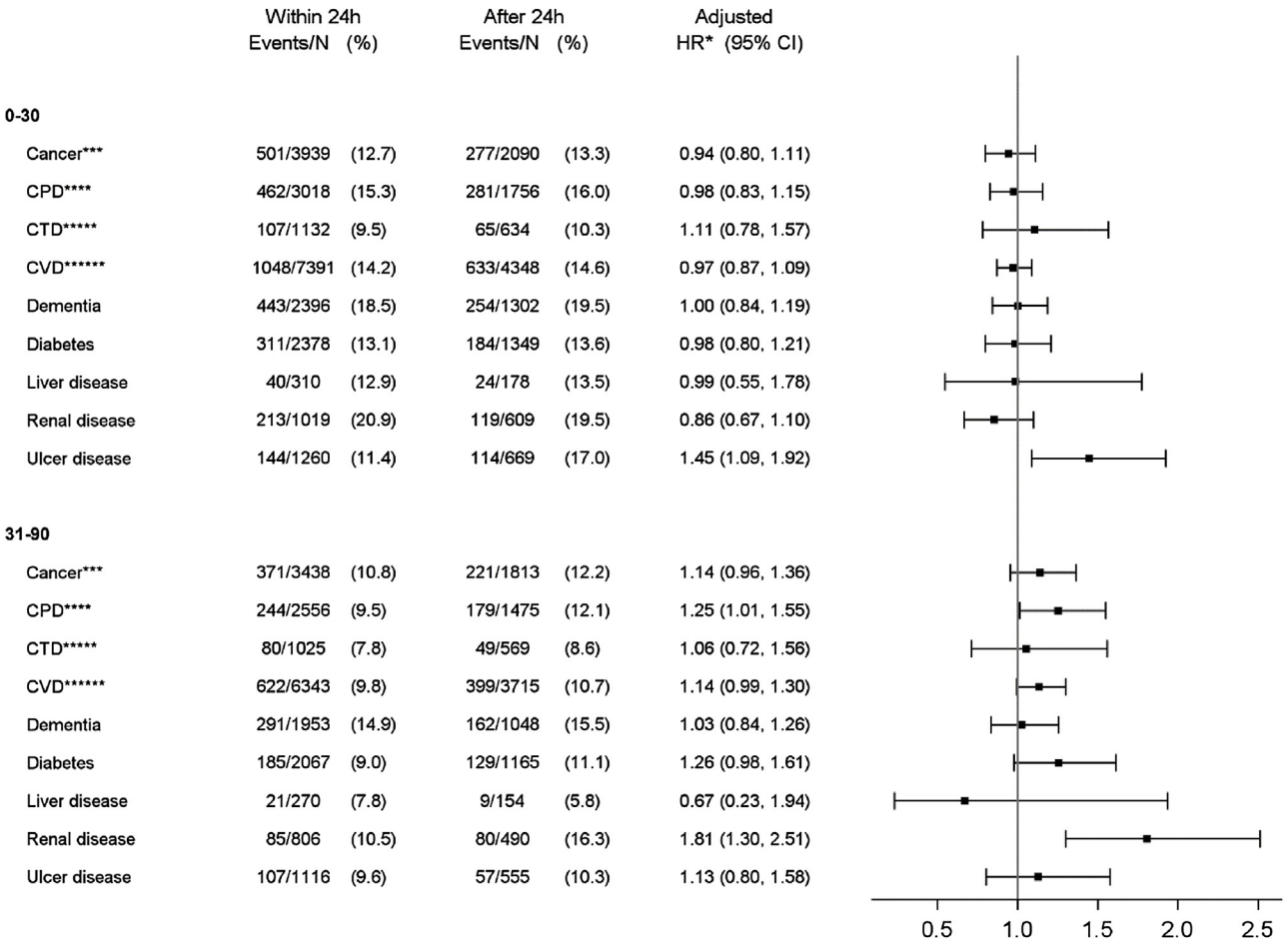

Fig. 5. Delay of >24 vs ≤24 h according to specific comorbidities**.
* Adjusted for age, gender, BMI, type of fracture, type of surgery, housing condition, marital status, use of anticoagulation drugs, psychiatric drugs, NSAIDs, steroids and the comorbidity groups in CCI expect for the stratified group. ** Hemiplegia and AIDS are not presented due to few observations. *** Cancer including any tumor, leukemia, lymphoma, metastatic solid tumor. **** Chronic pulmonary disease. ***** Connective tissue disease. ****** Cardiovascular disease including myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular disease.

delay ≤24 h and patients with renal disease having a surgery delay more than 24 h had an adjusted HR of 1.69 (95% CI 1.23 ; 2.31) for 31–90-days mortality than patients with a surgery delay ≤24 h.

Discussion

In this nationwide cohort study of 36,552 hip fracture patients we found for the first time an association between surgery delay and 30-days mortality in hip fracture surgery patients with none and medium level of comorbidity, whereas no such association was observed among hip fracture patients with high comorbidity level. In addition, surgery delay is associated with one year increased risk of dying in both patients with and without comorbidity prior surgery.

Strength and limitations

The strengths of this study include the use of prospectively collected data from national public registers and databases characterized by a high data validity [9,11,16], as well as complete follow up of all patients. In addition, we were able to control and stratify for a wide range of covariates that may potentially have an impact on the association between surgery delay and mortality and the recent study period (2010–2015) means that the study findings reflect current clinical practice, including very recent of current surgical and anesthetic techniques, devices and clinical guidelines. The primary limitation was the risk of residual or unaccounted confounding as is often the case in observational studies. Hence, we lacked data on socioeconomic factors and life-style factors such as alcohol and smoking, which could at least in theory confound the association between surgery delay and mortality. In addition, misclassification of comorbidity may have occurred, e.g. due to lack of data on psychiatric diseases and severity of some diseases such as diabetes and kidney failure. We did not have information on the specific reasons for surgery delay, however, it is probably likely to be medical for many patients with high comorbidity, and due to lack of surgical capacity for the majority of patients with no comorbidity prior to surgery.

Comparison with previous literature and possible explanations of our finding

Until now, several studies have investigated the association between surgery delay and mortality, but no studies, to our knowledge, investigated the association between surgery delay and mortality stratified on comorbidity, which is what distinguish this study from other studies. By this, our study gives a different perspective to the discussion about surgery delay. Further, most studies failed to adjust for factors as comorbidity, BMI and drug use, while we adjust for those in our study. This can be an explanation of why Nyholm et al. shows a significant association at the 12-, 24- and 48 h threshold on 0–30-days mortality [8] and

Bretherton et al. reported a significant association of the 12 h surgery delay and 0–30-days mortality, while we in our study find a borderline significant association at the 24 h threshold on the 0–30-days mortality. This suggest, that these variables have a substantial impact when investigating the association between surgery delay and mortality. Previous studies are also using older data, than the data we use in this study, thus they may not include patients treated according to current clinical guidelines. The difference between the results from former studies and this study can also suggest that the preoperative optimization and treatment for hip fracture patients have changed since then.

That patients with none/medium level of comorbidity are more effected of surgery delay than patients with high level of comorbidity may seem as a surprising founding. One explanation for this could be that sicker patients may benefit from a delay in order to optimize their medical condition while there is no theoretical benefit for healthier patients to wait for surgery. Rather, for the healthy patients there is the potential for increased complications and poor outcome [5].

A common reason for operative delay include the lack of surgical capacity at the operating room and/or surgical personnel [5]. Selection of patients for delay might not be correct. Given that high comorbidity patients are delayed due to medical reasons they will receive medical optimization. Patients without comorbidity might be more often selected to wait for surgery because these are considered to be “healthy” and can wait. A fundamental misunderstanding may lead to the assumption that healthy patients will not be harmed if they are delayed, because they are healthy. Our study suggest, that such understanding is basically not true for hip fracture patients and it shows that there is no harm for sick patients to be meaningfully delayed while healthy patients may be harmed by a delay. In a review of available literature Lewis et al. suggest a similar understanding. They suggest that an early surgery is appropriate in the relatively fit patient (ASA 1 or 2) with a fracture of the hip, probably within 12 h to 48 h. However, patients with an ASA score of 3 or 4 should allow surgery to be delayed to allow the general condition of the patient to be improved and this decision should not be classed as a fault in management [17]. Hip fracture patients are defined as healthy in our study if they did not have hospital contact for any of the 19 diagnoses included in the CCI and recorded in the DNPR. However, these patients are in general considered to be frail, functionally dependent, have a high prevalence of cognitive impairment, and could have underlying conditions such as dehydration, low kidney function, inflammation which does not necessary require hospital contact and is thus difficult to account with data from the DNPR. Further, patients with known comorbidity often receive organized help at home from nurses, which is not the case for the healthy patients. While waiting for help at home to be organized after discharge, they medical condition deteriorate increasing the risk of dying. Hypothetical, an un-constructive use of the delay in the less vulnerable patients, compared to patients with a known high comorbidity burden at the time of surgery, could lead to an association between delay in surgery and mortality in the less vulnerable patients both in short- and long-term period after surgery.

Clinical implications

The study indicates, that clinicians at the hospital have to continuously target treatment to not only patients with high level of comorbidity, but also hip fracture patients without known comorbidity prior surgery.

Conclusion

There was an association between surgery delay and 30-days mortality in hip fracture surgery patients with none and medium level of comorbidity, whereas no such association was observed among hip fracture patients with high comorbidity level. Surgery delay is associated with one year increased risk of dying in both patients with and without comorbidity prior surgery.

Conflict of interest

Buket Öztürk, Søren P. Johnsen, Niels Dieter Röck, Lars Pedersen and Alma B. Pedersen declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.injury.2018.12.032.

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