**ORIGINAL PAPER**

# Comorbidity and mortality after hip fracture in nineteen thousand six hundred and eighty two patients aged eighteen to sixty five years in Denmark from 1996 to 2012

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## Abstract

**Purpose** This nationwide study assessed associations between comorbidity and mortality after hip fracture in young and middle-aged patients.

**Methods** Data on 19,682 patients aged 18 to 65 years were extracted from Danish registries out of 154,047 patients who experienced a hip fracture between 1996 and 2012. Mortality and comorbidity were assessed using information on vital status, hospital admissions, and prescriptions.

**Results** Of the 19,682 patients 17,722 (90.0%) were middle-aged (40–65 years) and 1960 (10.0%) were young (18–39 years). The 30-day mortality rates were 3.2% ($n = 570$) and 1.6% ($n = 32$), respectively. Indicators of multi-trauma (hazard ratio (HR), 3.5 95% confidence interval (CI) [1.6–7.8], $n = 2056$) and having diabetes (HR, 4.4 [1.2–11.3], $n = 59$) and heart disease (HR, 4.4[1.3–14.8], $n = 57$) increased 30-day mortality in the young patients, while having cancer (HR, 5.0 [4.2–5.9], $n = 1958$) increased 30-day mortality in the middle-aged patients.

**Conclusion** Heart disease and diabetes were associated with high mortality in the young patients while having cancer was associated with high mortality in the middle-aged patients.

**Abbreviations**

| | |
|---|---|
| HR | Hazard ratio |
| CI | Confidence interval |
| ICD-10 | International classification of diseases |

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## Introduction

Hip fractures present a challenge to the worldwide health care system and patients who suffer from a hip fracture often have excess morbidity and mortality [1, 3]. Factors such as age, sex, anaemia, high Charlson Comorbidity Index, high American Society of Anesthesiologists (ASA) score, and dementia have all been related to mortality [14, 20]. Hip fractures among elderly patients are generally sustained in falls, whereas hip fractures in a younger population more often are caused by high-energy trauma [10, 17, 26]. The mortality after hip fracture has been heavily investigated among the elderly population. However, studies on hip fracture-related mortality among younger adults aged < 65 years are relatively scarce [27]. Young patients present a challenge in hip fracture treatment with a high incidence rate of post-surgical complications and a re-operation rate approaching 20% [30].

Until now, only a few nationwide population-based studies of mortality after hip fracture in younger patients have been published [15, 16, 32]. We hypothesize that both young and middle-aged patients below 65 years have a higher mortality rate after hip fracture compared to the general population, and that comorbidity affects mortality in both age groups. Hence, this study assesses the mortality after hip fracture and the association with comorbidity in young and middle-aged patients using a large sample of patients from the Danish National Patient Register.

## Materials and methods

### Study population

In the Danish National Patient Registry, we identified all patients aged between 18 and 65 years who were admitted with a fractured hip with the following ICD-10 codes: DS720 (femoral neck), DS721 (pertrochanteric), and DS722 (subtrochanteric) in Denmark during the period January 1, 1996 to December 31, 2012. Patients who appeared more than once during the period due to a contralateral fracture or to subsequent hip fractures were included with the index fracture only. Deaths registered in the Danish Registries from time of hip fracture in the period Jan 1, 1996 to the end of follow-up as of Dec 31, 2012 were included as the primary outcome variable.

We included a total of 19,682 patients between 18 and 65 years of age subsequently separated into a young group aged between 18 and 39 years and a middle-aged group between 40 and 65 years old. We included sex, age, and comorbidity in the form of groupings from the Charlson Comorbidity Index (CCI), which was coded based on the method described by Quan et al. [24]. Comorbidity was assessed by ICD-10 codes registered in the National Patient Registry before the time of hip fracture. The following comorbidity groups were included in the study: heart disease, cerebrovascular disease, peptic ulcer disease, chronic pulmonary disease, rheumatic disease, renal disease, liver disease, cancer, diabetes mellitus, hemi/paraplegia, and HIV/AIDS (Supplementary Table 1). Furthermore, to adjust for alcoholism or concurrent traumas, indicators of these conditions were included in the analyses (Supplementary Tables 2 and 3).

### National patient registries

The Danish Civil Registration System is a database where all Danish citizens are registered by a unique ten-digit civil registration number. The unique civil registration number makes it possible to retrieve information on individuals from a selection of national registries [29]. The Danish National Patient Register covers all somatic hospital admissions [18]. The Danish National Prescription Database includes information on all prescription drugs sold in Denmark since 1994 [13]. Data for calculating annual mortality rates in both men and women from the general Danish population in the years 1996–2012 were obtained from Statistics Denmark's website: https://dst.dk/da/Statistik/statistikbanken.

### Statistics

Continuous data were presented as means with standard deviations (SD), categorical data as numbers and percentages (%). For comparison of variables between age groups, student $t$ tests, chi squared tests, or Fischer's exact tests were applied when appropriate. Cox regression models were used for computing 30-day and one year hazard ratios for all-cause mortality with 95% confidence intervals for both univariate (unadjusted) and multivariate (adjusted) analyses. The multivariate regression models were based on variables significant at a 5% level by univariate analysis as well as sex and age. The proportional hazards assumption was assessed graphically plotting Schoenfeld residuals of all included variables. No major violations were detected. $P$ values less than 0.05 were considered statistically significant.

## Results

Among the 19,682 patients aged 18–65, 90% ($n = 17,722$) were middle-aged (40–65 years) and the remaining 10% ($n = 1960$) were young (18–39 years). Among the young patients, there was a higher proportion of males (77.24%) compared to females, in contrast to the even distribution of sex in the middle-aged patients (50% males). Also, the middle-aged patients had a higher prevalence of all comorbidities dominated by heart disease and indicators of excess use of alcohol (Table 1). In contrast, the young patients were more likely to be admitted with concurrent trauma and fractures besides the hip fracture and the most frequent comorbidities were hemi/paraplegia, diabetes mellitus, and heart disease (Table 1).

The young patients had a 30-day mortality rate of 1.6% ($n = 32$) and a one year mortality rate of 3.9% ($n = 77$). The middle-aged patients had a 30-day mortality rate of 3.2% ($n = 570$) and a one year mortality rate of 12.8% ($n = 2259$). For comparison the age-matched background population had 30 day mortality rates for individuals 18 to 39 years of 0.0063%, and 40 to 65 years of 0.05% and one year mortality rates of 0.075% and 0.59%, respectively.

Comorbidity was more frequent in the middle-aged patients (45.5%) compared to the young patients (14.4%) (Table 1). In the young patients, indicators of multi-trauma (adjusted HR, 3.5 [1.6–7.8]), diabetes mellitus (diabetes mellitus adjusted HR, 4.4 [1.2–11.3]), and heart disease (heart

**Table 1** Baseline characteristics of hip fracture patients aged 18–65 years in Denmark, 1996 to 2012

|  | Middle-aged (40–65 years) | Young (18–39 years) | P |
| --- | --- | --- | --- |
| Subjects | 17,722 (90.0) | 1960 (10.0) | |
| Age (years) mean (SD) | 56.28 (6.2) | 29.87 (6.6) | N/A |
| Sex (males) | 8856 (50.0) | 1514 (77.2) | < 0.0001 |
| Femoral neck (DS720) | 10,301 (58.1) | 1126 (57.2) | 0.5 |
| Pertrochanteric (DS721) | 5601 (31.6) | 475 (24.2) | < 0.0001 |
| Subtrachanteric (DS722) | 1820 (10.3) | 359 (18.3) | < 0.0001 |
| Any comorbidity | 8070 (45.5) | 282 (14.4) | < 0.0001 |
| HIV/AIDS | 39 (0.2) | 3 (0.2) | 0.2 |
| Cerebrovascular disease | 1736 (9.8) | 30 (1.5) | < 0.0001 |
| Hemi/paraplegia | 254 (1.4) | 62 (3.2) | < 0.0001 |
| Chronic pulmonary disease | 1554 (8.8) | 47 (2.4) | < 0.0001 |
| Renal disease | 326 (1.8) | 16 (0.8) | 0.001 |
| Rheumatic disease | 441 (2.5) | 10 (0.5) | < 0.0001 |
| Peptic ulcer disease | 1021 (5.8) | 19 (1.0) | < 0.0001 |
| Diabetes mellitus | 1591 (9.0) | 59 (3.0) | < 0.0001 |
| Heart disease | 3659 (20.7) | 57 (2.9) | < 0.0001 |
| Liver disease | 1276 (7.2) | 44 (2.2) | < 0.0001 |
| Cancer | 1958 (11.1) | 36 (1.8) | < 0.0001 |
| Alcohol medication | 3260 (18.4) | 171 (8.7) | < 0.0001 |
| Alcohol-related admission | 3949 (22.3) | 192 (9.8) | < 0.0001 |
| Other fractures | 2148 (12.1) | 756 (38.4) | < 0.0001 |
| Traumas w/o fractures | 1339 (7.6) | 544 (27.7) | < 0.0001 |

Values are frequency measured in absolute numbers and (%) unless otherwise stated. *SD* standard deviation. *P* values were calculated with Chi-square tests or Fisher's exact test where appropriate

disease adjusted HR, 4.4 [1.3–14.8]) were associated with increased 30-day mortality (Fig. 1). In contrast, in the middle-aged patients, having cancer was associated with the largest increase in 30-day mortality (adjusted HR, 5.0 [4.2–5.9]). Furthermore, indicators of alcoholism (adjusted HR, 1.7 [1.4–2.1]) and liver disease (adjusted HR, 1.7 [1.3–2.2]) were also associated with a modest increase in 30-day mortality (Fig. 2). For both young (adjusted HR, 13.7 [7.5–25.1]) and

middle-aged patients, cancer was associated with the largest increase in one year mortality (young adjusted HR, 13.7 [7.5–25.1], middle-aged adjusted HR, 7.3 [6.7–7.9]) (Tables 2 and 3). Other comorbidities such as renal disease in the young (adjusted HR, 4.4 [1.4–14.4]) and liver disease or renal disease in the middle-aged patients (liver adjusted HR, 1.9 [1.6–2.1]; renal adjusted HR, 1.8 [1.4–2.2]) associated with a modest increase in one year mortality.

**Fig. 1** 30-day hazard ratios for death in the younger patients (18–39 years). Dots or squares represent the hazard ratio (HR) and lines represent 95% confidence intervals. The HRs are on logarithmic scale
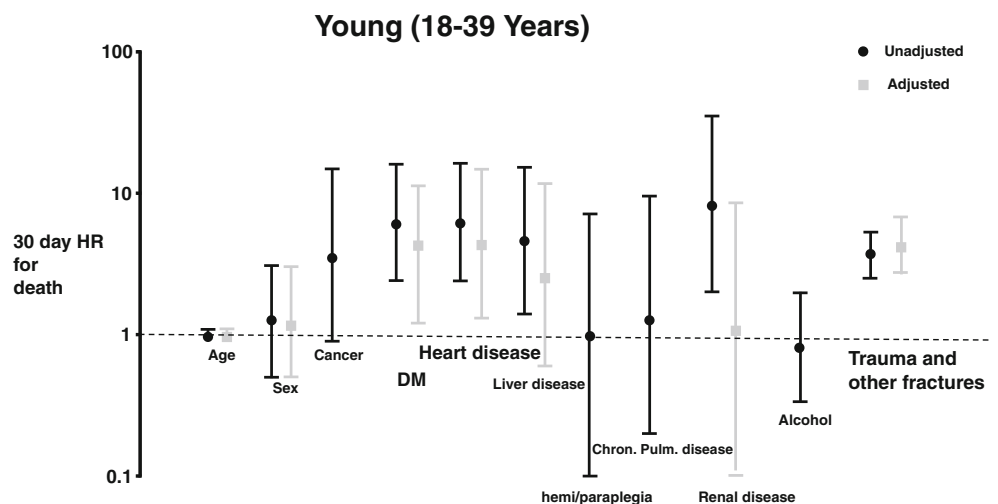
**Fig. 2** 30-day hazard ratios for death in the middle-aged patients (40–65 years). Dots or squares represent the hazard ratio (HR) and lines represent 95% confidence intervals. The HRs are on logarithmic scale

## Discussion

The most important finding in this nationwide study of almost 20,000 patients aged 18–65 years, is that comorbidity was associated with mortality after hip fracture in both young and middle-aged patients. In the young patients, heart disease and diabetes associated with the highest risk estimates for 30-day mortality, also when adjusting for indicators of multi-trauma, while having cancer was associated with the highest risk estimates in the middle-aged patients. Our findings support the notion that hip fractures among young patients present a real risk and additionally, that certain comorbidities need to be taken into consideration in the care of the young and middle-aged patients. An integrated multidisciplinary model as introduced for the elderly by orthopaedic units in Europe [5, 7] is warranted.

The mortality rates after hip fracture in the middle-aged and the young patients are almost ten times as high as in the same age groups in the background population. Thus, experiencing the trauma of a hip fracture increases mortality as for the elderly population [21]. Also, these patients could be selected by their comorbid conditions that increase the risk of hip fracture such as it has been proven in studies of the elderly population [4]. However, it is plausible that certain comorbid conditions have impact on mortality in one age group and not in

**Table 2** Comorbidity and 1-year mortality in young patients

| Young (18–39 years) | Unadjusted HR (95% CI) | P | Adjusted HR (95% CI) | P |
|---|---|---|---|---|
| Age | 1.1 (1.0–1.1) | < 0.0001 | 1.1 (1.0–1.1) | 0.009 |
| Sex | 0.6 (0.4–0.9) | 0.02 | 0.9 (0.5–1.6) | 0.7 |
| Alcoholism | 1.8 (1.1–3.1) | 0.03 | 1.6 (0.9–2.8) | 0.1 |
| Other fractures and traumas | 1.2 (0.8–1.9) | 0.4 | – | – |
| Cancer | 15.8 (9.1–27.5) | < 0.0001 | 13.7 (7.5–25.1) | < 0.0001 |
| Diabetes mellitus | 5.2 (2.7–10.1) | < 0.0001 | 2.1 (1.0–4.5) | 0.06 |
| Heart disease | 5.4 (2.8–10.5) | < 0.0001 | 2.4 (1.1–5.7) | 0.04 |
| Liver disease | 4.7 (2.1–10.1) | 0.0001 | 1.0 (0.4–2.8) | 0.9 |
| Hemi/paraplegia | 1.7 (0.6–4.6) | 0.3 | – | – |
| Chronic pulmonary disease | 3.5 (1.5–8.0) | 0.0003 | 2.5 (1.0–6.2) | 0.04 |
| Renal disease | 10.0 (4.0–24.8) | < 0.0001 | 4.4 (1.4–14.4) | 0.01 |
| Peptic ulcer disease | 6.0 (2.2–16.3) | 0.0005 | 3.3 (1.2–9.3) | 0.02 |
| Rheumatic disease | – | – | – | – |

Alcoholism includes both alcohol medication and alcohol-related admission. Only significant variables from the unadjusted analyses presented in Fig. 1 along with sex and age were included in the adjusted analysis. *HR* hazard ratio, *CI* confidence interval

**Table 3** Comorbidity and 1-year mortality in middle-aged patients

| Middle-aged (40–65 years) | Unadjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
|---|---|---|---|---|
| Age | 1.0 (1.0–1.0) | < 0.0001 | 1.0 (1.0–1.0) | 0.0009 |
| Sex | 1.0 (1.0–1.1) | 0.4 | 1.2 (1.1–1.3) | < 0.0001 |
| Alcoholism | 1.6 (1.5–1.7) | < 0.0001 | 1.4 (1.2–1.5) | < 0.0001 |
| Other fractures and traumas | 0.9 (0.8–1.0) | 0.1 | – | – |
| Cancer | 7.0 (6.4–7.6) | < 0.0001 | 7.3 (6.7–7.9) | < 0.0001 |
| Diabetes mellitus | 1.6 (1.4–1.8) | < 0.0001 | 1.4 (1.2–1.5) | < 0.0001 |
| Heart disease | 1.5 (1.4–1.6) | < 0.0001 | 1.1 (1.0–1.2) | 0.07 |
| Liver disease | 2.3 (2.0–2.5) | < 0.0001 | 1.9 (1.6–2.1) | < 0.0001 |
| Hemi/paraplegia | 0.8 (0.5–1.2) | 0.2 | – | – |
| Chronic pulmonary disease | 2.0 (1.8–2.2) | < 0.0001 | 1.6 (1.4–1.8) | < 0.0001 |
| Renal disease | 2.5 (2.0–3.1) | < 0.0001 | 1.8 (1.4–2.2) | < 0.0001 |
| Peptic ulcer disease | 1.7 (1.5–1.9) | < 0.0001 | 1.2 (1.0–14) | 0.04 |
| Rheumatic disease | 0.9 (0.7–1.2) | 0.5 | – | – |

Alcoholism includes both alcohol medication and alcohol-related admission. Only significant variables from unadjusted analyses presented in Fig. 2 along with sex and age were included in the model. *HR* hazard ratio, *CI* confidence interval

another as shown in the present study. Lastly, age is a very strong predictor of mortality after hip fracture even in the elderly [7].

Compared to elderly patients aged 65 years and above who have an increasing burden of comorbidity over time [3], the middle-aged patients in our study population had a lower overall comorbidity burden. Furthermore, the most important comorbid condition affecting mortality in the middle-aged patients was having a cancer diagnosis while heart- and peptic ulcer-disease only had modest associations with increased mortality. In an elderly population, comorbid conditions inferring a higher ASA-score or more severe osteoporosis which both have effect on mortality [4] would be expected to have the strongest association with increased mortality. Therefore, distinguishing between the elderly and the middle-aged patients in relation to the peri-operative care of comorbid conditions is warranted.

Diabetes mellitus and heart disease were among the most frequent comorbidities in the young patients and associated with the highest risks of 30-day mortality after hip fracture in our study. However, the number of patients are quite low if calculated per year (59 and 57 over a period of 13 years) with an average of less than five young patients having these comorbidities per year in Denmark. Thus, our results should be interpreted in the light of the relatively low comorbidity burden in the young patients in our population-based study compared to other studies [2, 28, 31]. Of note, patients aged 20–40 years from a nationwide study in Asia also had low frequencies of comorbidity [15].

Patients with type 1 diabetes have increased risk of hip fractures compared with both patients with type 2 diabetes and matched control individuals [8], and diagnosis at an early age as well as the duration of diabetes have been identified as risk factors for fractures in general [6]. A recent population-based study showed that low body mass index and diabetes have an effect on the incidence of hip fractures, but also that these two factors interact [9]. In a population of 50 years and above, also patients with type 2 diabetes have increased post-fracture mortality compared to non-diabetic patients [19]. Generally, in patients with diabetes, coronary heart disease is more common [22]. However, for comparison to our study, there is limited information from studies assessing the frequency of coronary heart disease in a younger population of patients after hip fracture. Thus, it may not be surprising that having diabetes and heart disease could increase mortality after hip fracture in young patients.

In the middle-aged patients, the most frequent comorbidity was heart disease, which is also corroborated by an Estonian population-based cohort study that found congestive heart disease to be the most common comorbidity among patients above 50 years of age [11]. Furthermore, a Danish population-based study showed cerebrovascular disease, cancer, and congestive heart failure to be the most frequent [12]. However, in the middle-aged patients, having heart disease was not associated with increased mortality. In contrast, the less prevalent comorbidity cancer increased both the 30-day and one year hazard ratio for death. Patients with cancer who experience a hip fracture might be more frail patients who already have an increased risk of death before they experience a hip fracture. Of note, one year mortality was affected quite dramatically by having cancer in the young patients, where the same issue of frailty might apply.

Up to 50–60% of multi-trauma patients die from their injuries alone prior to arrival at a hospital [23], and this could lead to selection bias in our study. We adjusted for indicators of multi-trauma such as ICD-10 codes for other concurrent fractures and traumas in the multivariate regression analysis but we cannot eliminate all potential bias. Also, we adjusted for patients who

suffer from alcoholism, as they are predisposed to cancer, liver cirrhosis, and alcohol-related injuries which all lead to increased mortality [25]. Another study reported about a quarter of both young and middle-aged patients to be self-reported high-volume drinkers [2]. We found less than 10% alcohol-related admissions and or use of alcohol medication among the young patients and 18–22% in the middle-aged patients. Thus, we could have underestimated the association between alcohol and mortality in the young patients.

Since the study was register-based, we had no loss to follow up but at the same time, limitations such as no direct information on surgery, peri-operative management, complications, anaesthesia, smoking habits, alcohol consumption, under-weight or obesity, or exercise. Confounding by these factors can therefore neither be evaluated nor ruled out. Of note, concerning the timing of surgery, small delays have not proven to affect mortality [33]. Overall mortality was obtained by registry linkage. The Danish Civil Registration system has a very high validity, and the risk of misclassification is considered minimal [29]. The main strength of the study is the large number of patients covering all registered Danish patients between 18 and 65 years with a hip fracture over a period of 13 years. Thus, the study is both representative of the Danish population and generalizable for similar populations.

In conclusion, both young and middle-aged patients experience increased mortality after hip fracture compared to the background population. Heart disease and diabetes were associated with high mortality in the young patients while having cancer was associated with high mortality in the middle-aged patients. Attention to patients with these comorbid conditions is warranted to prevent deaths in young and middle-aged patients after hip fracture.

## Compliance with ethical standards

**Conflict of interests** The authors declare that they have no conflict of interest.

**Ethical approval** According to Danish law, ethical committee approval is not required for this type of observational study. The data were obtained through secure remote access to Statistics Denmark (ref. 704670). The study was approved by the Danish Data Protection Agency (2012-58-0004)/local number BBH-2014-050.

**Informed consent** For observational register-based studies, formal consent from patients is not required.

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