Does impact of comorbidity on 1-year mortality after hip fracture differ by gender? A NOREPOS study

Brit Solvor Lyse Riska, MD[1,2], Lisa Forsén, PhD[1,2], Tone K Omsland, PhD[3], Anne Johanne Søgaard, PhD[2], Haakon E Meyer, MD PhD[2,3], Kristin Holvik, PhD[2]

[1] Norwegian National Advisory Unit on Women's Health, Oslo University Hospital, Oslo, Norway
[2] Department of Non-Communicable Diseases, Norwegian Institute of Public Health, Oslo, Norway
[3] Department of Community Medicine and Global Health, Institute of Health and Society, University of Oslo, Oslo, Norway

Correspondence: Kristin Holvik, Norwegian Institute of Public Health, P. O. Box 4404 Nydalen, 0403 Oslo, Norway. Telephone: +47-21 07 83 97. E-mail: Kristin.holvik@fhi.no

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Ethical approvals

The study and the data linkages were approved by the Norwegian Data Protection Authority, the Regional Committee for Medical and Health Research Ethics, the Directorate of Health and Statistics Norway.

Impact statement

We certify that this work is confirmatory of recent novel clinical research by Kannegaard et al. Age Ageing 2010; 39: 203-9. The potential impact of this research on clinical care and health policy includes the need for an increased awareness of the vulnerability of the male hip fracture patient. Based on population-wide data we show that male hip fracture patients both have more comorbid conditions and higher mortality than female hip fracture patients. However, our study suggests that the excess mortality after a hip fracture also is evident in men with no comorbidity.

ABSTRACT

BACKGROUND: Excess mortality after hip fracture is higher in men than in women.

OBJECTIVE: To study whether comorbidity differs between male and female hip fracture patients and to what degree gender differences in comorbidity may explain the higher excess mortality in men.

DESIGN: Population-based matched cohort covering the population 50 years and older in Norway.

SETTING: Specialist healthcare (patients) and general population (controls)

PARTICIPANTS: All hip fracture patients aged 50 years and older 2005-2008 (n=32,175) and individuals without hip fracture matched 3:1 to the patients on gender, age and county of residence (n=96,410).

MEASUREMENTS: Comorbid diagnoses were recorded during the hospital stay. Relative and absolute excess 1-year mortality in hip fracture patients according to gender and Charlson comorbidity index (CCI) were investigated in Cox regression and linear regression, respectively.

RESULTS: Despite lower age (mean 78.7 vs. 81.7 years), men had higher comorbidity than women. Compared with controls, hazard ratios (HR) for death in patients with CCI 2+ was 6.5 (95% CI 6.2-6.9) in women and 7.8 (95% CI 7.3-8.3) in men. Estimated risk of dying within one year in patients with CCI 2+ compared with controls was 44% vs. 11% for women, and 53% vs. 12% for men. Relative one-year mortality in men compared with women was HR 2.0 (95% CI 1.9-2.1), which was attenuated to HR 1.8 (95% CI 1.7-1.8) when adjusting for comorbidity.

CONCLUSION: Men had higher comorbidity than women. However, this did not explain the gender difference in excess mortality after hip fracture. Men who fracture their hip

represent an especially vulnerable subpopulation, even when there is no apparent comorbidity, and warrant special attention in follow-up and care.

Key words: Hip fracture, mortality, comorbidity, gender differences, Charlson comorbidity index

INTRODUCTION

Norway has one of the highest incidence rates of hip fracture in the world,[1] with around 9,000 hip fractures occurring every year.[2] High age and female gender are strong risk factors. Men account for 30% of the hip fractures.[2] Both men and women have excess mortality after hip fracture,[3, 4] but there is evidence to suggest that men who fracture their hip are in worse health condition.[5-7] Male gender is a strong and consistent predictor of mortality after hip fracture.[4, 7-12] Also when taking into account the lower life expectancy in men,[13] men have higher excess mortality after hip fracture.[3, 4, 14, 15]

Comorbidity may be seen as the total burden of illnesses. Illnesses vary in their nature, extent and severity. Comorbidity is associated with increased mortality in hip fracture patients,[5, 10, 16] but the contribution of pre-existing illness to mortality after hip fracture is unresolved. In register data from Sweden, post-hip fracture mortality was largely related to the patients' comorbidity.[17] In contrast, a Danish study concluded that only a minor proportion of mortality could be attributed to pre-existing comorbidity.[18] In a meta-analysis of eight population-based European cohorts, the effect of hip fracture on mortality was only slightly attenuated when taking major chronic diseases into account.[15]

Few studies have looked in detail at the contribution of gender differences in comorbidity to differences in excess mortality after hip fracture, and the findings are ambiguous. In national register data from Denmark, the higher mortality in male patients was not affected by gender differences in comorbidity.[5] We aimed to examine whether this was the case also in older adults in Norway, a population with many similarities, including high life expectancy and a high fracture incidence. The aim of this study was to explore whether comorbidity differs between male and female hip fracture patients, and to which degree gender differences in comorbidity may explain the higher excess mortality in men after hip fracture.

METHODS

Study population and demographic data

We retrieved data from electronic patient administrative systems on all admissions with hip fracture to hospitals in Norway from the NORHip database established by the Norwegian Epidemiologic Osteoporosis Studies (NOREPOS).[19] For the current study we included all patients 50 years and older who suffered their first hip fracture during 2005-2008 (n=32,175; Supplementary Figure S1). The source population for controls was identified in the Norwegian Population and Housing Census 2001 (Statistics Norway) and comprised Norwegian residents 50 years and older by 2008 who had not suffered a hip fracture during 1994-2004 (n=1,675,893). For each patient we drew three controls, matched to patients on birth year, gender and county of residence, and conditioned on being alive, residing in Norway and free of hip fracture on the patient's fracture date. Only 61 patients (0.2%) had fewer than three available controls, and a total of 96,410 matched controls were included. Data on birth year, gender, county of residence, marital status, immigration status, number of children and attained educational level were obtained from the Norwegian Population and Housing Census 2001. The National Registry provided dates of death or emigration.

Comorbidity

All concurrent diagnoses that were deemed relevant by the treating doctors during the hospitalization for hip fracture were available in NORHip, coded according to the International Classification of Diseases, 10th revision (ICD-10). These diagnoses enabled us to calculate the patients' individual Charlson comorbidity index (CCI) score.[20, 21] The index has been shown to be prognostic of mortality in hip fracture patients.[22-24] It is based on information about whether a patient has any of the diagnoses on a list of given conditions, and each condition is weighted according to severity (Supplementary Table S1). We calculated individual CCI scores using the Stata syntax written by V. Stagg,[25] truncated to 0, 1 or 2+. As such, a score of 0 indicates that none of the listed conditions were registered during the patient's hospital stay, a score of 1 indicates having one condition of less severity, and a score of 2+ reflects having two or more conditions of any severity, or one or more conditions of greater severity. Individual information about chronic diseases was not available in controls. The morbidity level of the controls reflects the distribution of morbidity in the general population of older adults without hip fracture.

Statistical analysis

Data management and statistical analysis was performed in Stata 14. Attained age was included as a continuous variable. We estimated adjusted proportions of death among hip fracture patients according to CCI score and specific comorbid diagnoses by analysis of variance (ANOVA), and used Cox proportional hazards regression to estimate survival in CCI categories relative to non-hip fracture controls within the genders. The patient's admission date was defined as entry date in the analysis for both the patient and his/her matched controls and end of follow-up was set to 365 days post-fracture. To quantify the risk of death on an additive scale we performed robust linear regression using the matched controls as reference category. We thus estimated the one-year risk of death as the constant in linear regression for the controls (reference), adjusted to mean age within each gender, and percentage points higher risk of dying in each CCI category as the beta coefficients in linear regression. We performed additional analyses stratified on age in tertiles. All regression models were adjusted for the matching variables (birth year, gender and county of residence). Proportions of deaths by specific diagnoses were also adjusted for the patient's total number of comorbid diagnoses. Additional adjustment for marital status (married/ widowed/other), immigrant status (defined as foreign-born with none or one Norwegian-born parent or Norwegian-born with two foreign-born parents), attained educational level (completed first year of secondary school or higher (≥10 years) vs. completed primary school or lower (≤9 years)) and having children (yes/no) in any of the above mentioned analyses gave only negligible changes to the estimates, and we have not presented these results. The significance level was set to 0.05 in all analyses.

RESULTS

Patient characteristics

Age at hip fracture ranged from 50-105 years and women were on average three years older than men (Table 1). A higher proportion of men were married, whilst more women were widowed. Men had higher education. Men also had a significantly higher average number of diagnoses registered during the hospital stay, and a higher proportion of the male patients had CCI 2+. While one in five women died within one year after the fracture, the corresponding proportion among men was one in three (Table 1).

Comorbidity and risk of death in hip fracture patients

Risk of dying within one year after hip fracture, adjusted for age and county of residence within the genders, increased by increasing CCI score (Supplementary Table S2). Among women with CCI 0, an adjusted proportion of 11% died within one year, whilst 24% and 41% died among those with CCI 1 and 2+. The corresponding incidence proportions in men were 22%, 38% and 52%, respectively.

A larger proportion of women had no CCI diagnosis registered, 52% vs. 45% in men (Supplementary Table S3). All comorbid diagnoses were more prevalent among men, except rheumatic disease. In women, dementia was the most prevalent diagnosis (12%), while chronic lung disease and dementia were equally prevalent in men (14%). The adjusted proportion of deaths within one year in patients with a dementia diagnosis was 36% in women and 57% in men. The proportion of deaths was higher among men for all registered CCI diagnoses (Supplementary Table S3).

Relative risk of death by gender and comorbidity

Compared with controls, there was a strong association between CCI score and one-year mortality in hip fracture patients of both genders (Table 2, Supplementary Figure S2). Hazard ratios (HR) increased through increasing CCI score but even patients without registered comorbidity (CCI 0) had increased HR (Table 2). There was statistical interaction between age and comorbidity ($p<0.001$ for both genders). Cox regression stratified by tertiles of age distribution, corresponding to 50-79, 80-86 and 87-105 years, revealed that the relative excess mortality due to comorbidity was highest at younger ages in both genders (Supplementary Table S4).

When comparing male and female hip fracture patients, men had an age-adjusted HR of 2.0 (95% CI 1.9-2.1) for death within one year compared with women. With comorbidity adjustment, HR was reduced to 1.8 (95% CI 1.7-1.8). Within levels of CCI, the HR in men compared with women was 2.3 (95% CI 2.1-2.5) at CCI 0, 1.9 (95% CI 1.7-2.0) at CCI 1 and 1.4 (95% CI 1.3-1.5) at CCI 2+. Among the matched controls, men had HR 1.4 (95% CI 1.3-1.5) compared with women.

Risk difference in death by gender and comorbidity

In linear regression, estimated risk of death within one year in the matched non-fracture controls was 11% in women and 12% in men, adjusted for age and county of residence within genders (Table 3). There was increasing one-year risk of death with increasing CCI level. The gender difference in excess risk of death in patients was mainly driven by the large difference between patients and controls, while the gender difference in added risk of death by increasing CCI in patients was small. The estimated risk difference between patients with CCI 2+ and patients with CCI 0 was 29 percentage points in both genders (Table 3).

DISCUSSION

This population-wide study of all patients hospitalized with a first hip fracture in Norway over a four-year period showed that men who suffered a hip fracture had more comorbidity than women. A higher comorbidity burden was associated with increased excess one-year mortality in both genders, and the association was even stronger in men. However, the gender difference in comorbidity did not explain the gender difference in one-year mortality.

It has been reported in many studies that excess mortality after hip fracture is higher in men,[3-5, 8, 9, 11, 12] despite men being younger when suffering a hip fracture. It has been proposed that higher prevalence and severity of pre-existing chronic diseases in men who suffer a hip fracture contribute to explaining their poorer prognosis. Comorbidity is a recognized predictor of mortality after hip fracture,[5, 10, 16] but its contribution is unresolved. In register data from Sweden, it was estimated that the majority of deaths in hip fracture patients were due to pre-existing illnesses.[17] In contrast, a patient register study in Denmark found that the excess mortality after hip fracture was only slightly attenuated (from HR 2.26 to HR 1.95) when taking into account CCI score. The authors concluded that the increased mortality appeared to be largely related to the fracture event itself.[18]

In our data, HR for one-year mortality was doubled in men compared with women. The gender difference in mortality was only slightly attenuated by taking into account comorbidity level, and it remained higher than that in the background population. This is in line with the finding of an age-adjusted 70% higher post-hip fracture mortality in men compared with women in Denmark, which was unaffected by adjustment for comorbidity.[5] These results suggest that other gender-related differences not accounted for by comorbid diagnoses contribute to the higher excess mortality in men after hip fracture. A recent study identified no gender differences in quality of in-hospital care for hip fracture defined by several process performance measures.[12] Use of bisphosphonates may reduce mortality.[26] The prevalence of use of these drugs after a hip fracture is low, and even lower in men.[27]

The statistical interaction between age and comorbidity revealed a greater relative effect of increasing comorbidity on excess mortality in younger hip fracture patients. In general, the excess mortality after hip fracture expressed by standardized mortality rates is higher at younger ages due to the lower background mortality.[4]

A strength of our study is that it is based on a nationwide database of hip fracture admissions to all hospitals in Norway, linked with national register data covering the whole population. All patients were included regardless of geographic area and socioeconomic position. We had data on all deaths and almost complete demographic data, both for the patients and the matched controls. Statistical power is high, giving precise results. A limitation is the lack of data on chronic diseases in the background population. The controls represented a random sample with the same age-, gender- and geographic distribution as the patients, reflecting the distribution of morbidity in the general population of older adults. In that respect, the clearly increased mortality in hip fracture patients with no registered comorbidity is remarkable.

The measure of comorbidity in the patient population is not ideal in terms of neither sensitivity nor specificity. The ICD-10 diagnoses codes used to define comorbidity were recorded during the hospital stay when the hip fracture was treated, and are expected to represent an underestimation of the true prevalence of comorbidity. Hospital routines require that diagnoses deemed relevant for the actual stay are recorded, but coding practices may partly be driven by the hospitals' financing system. Therefore, we do not expect to have captured the true level of comorbidity, which is a general problem when using comorbidity scores from administrative patient data.[28] However, for the current purpose, we do not expect that underestimation of comorbidity should differ systematically according to the patients' gender.

Our study shows that comorbidity places patients at particular risk of death post-hip fracture. This information should be used in the management of hip fracture patients to direct attention to comorbidities so that, with targeted care, an individual's mortality risk may be lowered. Many comorbidities are also associated with increased risk of suffering a hip fracture in the first place.[29, 30] As such, knowledge about comorbid conditions is not just important in inpatient management, but also for prevention purposes. Concerning prognosis, we have shown that men who fracture their hip are especially vulnerable, even when there is no apparent comorbidity, and they may warrant special attention in the follow-up. Although age-specific incidence rates of hip fracture have declined the last decades,[2] this decline has been lower in men than in women, and the future fracture burden is expected to increase due to an ageing population that continues to grow. Thus, there is a great need for improvement both in the prevention of fracture and in reducing post-fracture mortality, both in women and men.

Conclusion

Our study covering the population 50 years and older in Norway showed that men who suffered a hip fracture had higher comorbidity burden than women. Higher comorbidity scores were associated with increased excess one-year mortality in both genders, and the association was even stronger in men. However, the difference in comorbidity did not explain the gender difference in one-year mortality. Factors not accounted for by comorbid diagnoses, such as factors related to the fracture event itself or other aspects concerning follow-up and care of male patients might contribute to explain the higher excess mortality in men. Awareness is needed of risk factors such as poor nutritional status, sarcopenia, functional impairment, subsequent fall risk and postoperative complications. Men who fracture their hip represent an especially vulnerable subpopulation, even when there is no apparent comorbidity, and may warrant special attention.

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Authors' contribution: BSLR reviewed the literature, performed the data analyses and drafted the manuscript in collaboration with KH. LF has advised in statistical methods. TKO, AJS and HEM have critically revised the manuscript for intellectual content. All co-authors have read and approved the final manuscript.

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LEGENDS

Table 1. Crude characteristics of patients aged 50+ with incident hip fracture in Norway 2005-2008 [a]

	Women N=22,445	Men n=9,730
Age in years, mean (SD)	81.7 (9.4)	78.7 (10.6)
Married, %	35.1	60.7
Widowed, %	49.1	16.3
Immigrants [b], %	2.2	1.9
Secondary education [c], %	45.5	58.2
No children [d], %	23.5	23.8
Number of comorbid diagnoses [e], mean (SD)	2.2 (1.9)	2.4 (2.1)
CCI score, n (%)		
0	11,745 (52.3)	4,366 (44.9)
1	6,848 (30.5)	2,747 (28.2)
2+	3,852 (17.2)	2,617 (26.9)
Died within one year after hip fracture, %	21.0	32.5

SD: standard deviation; CCI: Charlson comorbidity index

[a] Demographic variables (marital status, number of children, immigration status, education) were obtained in the Population Census 2001; comorbidity information was obtained from the hospitalization with a hip fracture

[b] Immigrant: foreign born with none or one Norwegian born parent, or born in Norway with foreign born parents

[c] Completed first year of secondary school or higher (≥10 years) vs. completed primary school or lower (≤9 years). Missing information for 206 (1.0%) women and 88 (1.0%) men

[d] Missing information for 39 (0.2%) women and 26 (0.3%) men

[e] Diagnosis codes for external cause of injury (V-, W-, X-, and Y-codes in ICD-10), contact with health services (Z-codes in ICD-10), or femoral fractures (ICD-10 code S72) not included

Table 2. Hazard ratios with 95% confidence intervals for death within 1 year by Charlson comorbidity index score in hip fracture patients in Norway 2005-2008 compared with matched controls [a, b]

	Women			Men		
	n	**HR**	**95% CI**	**n**	**HR**	**95% CI**
Controls (ref.) [c]	67,278	1.0	-	29,137	1.0	-
Patients, CCI 0	11,745	1.5	1.4 - 1.6	4,366	2.6	2.4 - 2.8
Patients, CCI 1	6,848	3.2	3.0 - 3.3	2,747	4.5	4.2 - 4.9
Patients, CCI 2+	3,852	6.5	6.2 - 6.9	2,617	7.8	7.3 - 8.3

HR: Hazard ratio; CI: confidence interval; CCI: Charlson comorbidity index; ref.: Reference category

[a] Each control's survival was measured from the hip fracture date of his or her matched patient.

[b] Adjusted for age and county. All p-values < 0.001 within each gender

[c] CCI is available in patients only. Morbidity level in the control group represents the distribution of morbidity in the non-hip fracture background population

Table 3. Estimated one-year risk of death (%) with 95% confidence intervals for hip fracture patients in Norway 2005-2008 and matched controls by gender and Charlson comorbidity index score [a]

	Women			Men		
	n	**Risk (%)**	**95% CI**	**n**	**Risk (%)**	**95% CI**
Controls [b]	67,278	11	10-11	29,132	12	10-13
Patients, CCI 0	11,745	15	14-15	4,366	24	22-25
Patients, CCI 1	6,848	26	25-27	2,747	37	35-38
Patients, CCI 2+	3,852	44	42-45	2,617	53	51-55

CI: confidence interval; CCI: Charlson comorbidity index

[a] In controls, risk (%) of death within one year corresponds to the constant in linear regression at mean age (82 in women, 79 in men). In patients, risk (%) of death within one year is calculated by the constant + percentage points added risk expressed by beta coefficient in linear regression. Adjusted for age and county of residence. $p<0.001$ for all differences within the genders

[b] CCI is available in patients only. Morbidity level in the control group represents the distribution of morbidity in the non-hip fracture background population

LEGENDS TO SUPPLEMENTARY FIGURES

Supplementary Figure S1. Available hip fracture patients aged 50 years and older from patient administrative systems in hospitals in Norway 2005-2008 and control population in the Norwegian Population and Housing Census 2001

Supplementary Figure S2. One-year survival of hip fracture patients by gender and Charlson comorbidity index and matched controls without hip fracture, Norway 2005-2008. Adjusted for age and county [a]

[a] In all groups of hip fracture patients survival was statistically significantly lower ($p<0.001$) than that of the matched control group of the same gender