

Survival Times of Patients with a First Hip Fracture With and Without Subsequent Major Long-Bone Fractures

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Abstract

Objectives: Survival rates are poorer after a second hip fracture than after a first hip fracture. Previous survival studies have included in-hospital mortality. Excluding in-hospital deaths from the analysis allows survival times to be evaluated in community-based patients. There is still a lack of data regarding the effects of subsequent fractures on survival times after hospital discharge following an initial hip fracture. This study compared the survival times of community-dwelling patients with hip fracture who had or did not have a subsequent major long-bone fracture. Hazard ratios and risk factors for subsequent fractures and mortality rates with and without subsequent fractures were calculated.

Materials and Methods: Of 844 patients with hip fracture from 2000 through 2008, 71 had a subsequent major long-bone fracture and 773 did not. Patients who died of other causes, such as perioperative complications, during hospitalization were excluded. Such exclusion allowed us to determine the effect of subsequent fracture on the survival of community-dwelling individuals after hospital discharge or after the time of the fracture if they did not need hospitalization. Demographic data, causes of death, and mortality rates were recorded. Differences in mortality rates between the patient groups and hazard ratios were calculated.

Results: Mortality rates during the first year and from 1 to 5 years after the most recent fracture were 5.6% and 1.4%, respectively, in patients with subsequent fractures, and 4.7% and 1.4%, respectively, in patients without subsequent fractures. These rates did not differ significantly between the groups. Cox regression analysis and calculation of hazard ratios did not show significant differences between patients with subsequent fractures and those without. On univariate and multivariate analyses, age <75 years and male sex were risk factors for subsequent fracture.

Conclusions: This study found that survival times did not differ significantly between patients with and without subsequent major long-bone fractures after hip fracture. Therefore, all patients with hip fracture, with or without subsequent fractures, need the same robust holistic care. The risks of subsequent fractures should be addressed in patients with hip fracture and should be reduced where possible by education regarding fracture prevention and regular rehabilitation programs. Efforts should be made to decrease the rates of major long-bone fractures and their burdens, even though such fractures have only a minor effect on survival in community-dwelling individuals.

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Key words: hip fracture, mortality rate, risk factor, subsequent major long bone fracture, survival

Introduction

The number of hip fractures is increasing as populations age¹. The treatment of these fractures and their associated morbidity and mortality represent a major public health burden. Information to help prevent hip fractures and information regarding survival after hip fracture are important for providing optimal medical care. Berry et al.² have reported higher mortality rates and shorter survival times in patients with second hip fractures than in patients with first hip fractures. However, their analysis included in-hospital deaths. An analysis of the survival of patients with hip fracture after hospitalization, excluding in-hospital deaths, would clarify the consequences of fractures in community-dwelling individuals. Other subsequent fractures, such as major long-bone fractures, may also affect the survival of patients with hip fractures. There is still a lack of data regarding the effects of subsequent major long-bone fractures on the survival of community-dwelling individuals with hip fractures. Therefore, the present study compared the survival times of community-dwelling patients with first hip fractures who had or did not have subsequent major long-bone fractures. The risk factors for subsequent fracture and mortality causes were also studied.

Materials and Methods

Study Population

A total of 844 patients (109 men and 735 women) 55 years or older were included in this study. The medical records of all admitted patients in orthopaedic department from January 2000 through December 2008 were reviewed, and patients were included in the study if they had sustained a first hip fracture (intertrochanteric or femoral neck fracture) and if roentgenograms showing the fracture were available for review. Any subsequent major fractures of long bones were recorded. Patients were excluded if the fractures were due to pathological causes (e.g., primary or secondary tumor, metabolic bone disease) or high-energy

trauma (e.g., traffic accidents or falls from a greater than standing height) or if the hip fracture and a fracture of a major long bone were simultaneous. Patients were also excluded if they died before hospital discharge, died of cancer, or were lost to follow-up within 5 years after the last fracture. Because this study aimed to determine the effect of fractures on community-dwelling individuals after hospital discharge, patients were excluded if they died during hospitalization, from such causes as perioperative complications. The study protocol was approved by the institutional review board of our institution.

Study Groups

The 844 patients who sustained a first hip fracture were divided into 2 groups: 71 patients with subsequent fractures of major long bone (humerus, radius, ulna, femur, or tibia) and 773 patients without such fractures. Patients were not included if they subsequently sustained a contralateral hip fracture (femoral neck or intertrochanteric fracture) or another type of osteoporotic fracture. Patients were regularly followed up for the duration of the study period or until they died. **Figure 1** shows the fracture events in each group.

Baseline Data Collection

Patient baseline characteristics were obtained from the medical records. Demographic data were recorded at the time of the first hip fracture and included age group (55–74, 75–84, or >85 years), sex, time from first hip fracture to any subsequent major long-bone fracture (0–12, 12–24, 24–48, or >48 months), mechanism of injury, fracture category, mobility before the first hip fracture, and medical comorbidities, including osteoarthritis of the knee. Cause of death was recorded, as was the time of death (years) after discharge from hospitalization for the last fracture, or after the time of the last fracture if hospitalization was not required. Some patients with subsequent fracture required hospitalization. If any patient with subsequent fracture did not require hospitalization, the survival time was calculated from immediately away after the fracture event.

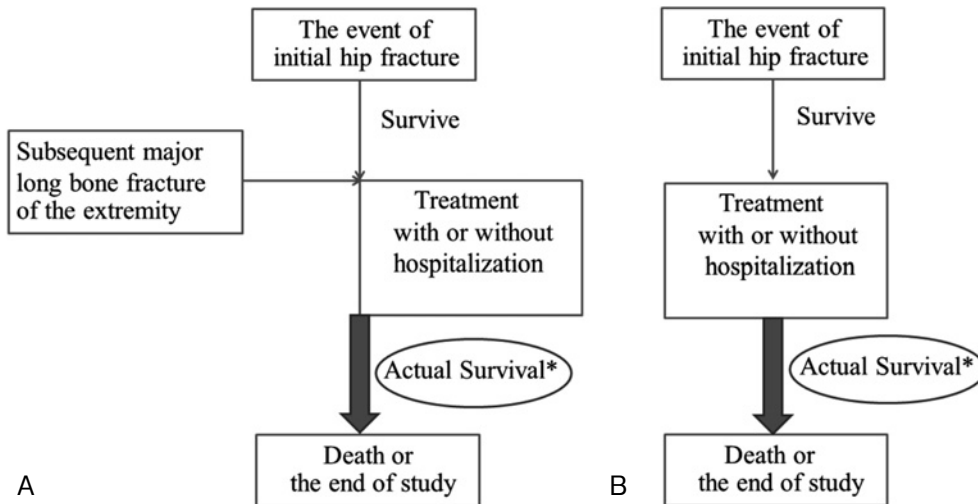


Fig. 1 Schematic flowchart showing events in patients A) with subsequent major long-bone fractures and B) without subsequent major long-bone fractures.

*Actual Survival is the survival time (years) after discharge from hospitalization for the recent fracture or the time after the recent fracture if hospitalization was not required.

Prefracture mobility was classified as follows: walking outside with or without an assistive device, walking inside with or without an assistive device, mobile with a wheelchair, or confined to bed. The following comorbid conditions were recorded: hypertension, neurological disease (Alzheimer's disease, Parkinson's disease, cerebrovascular accident, dementia), heart disease (arrhythmia, myocardial infarction, angina pectoris), respiratory disease (asthma, chronic bronchitis, chronic obstructive pulmonary disease), diabetes mellitus, osteoarthritis of the knee, renal disease, and eye disease (glaucoma, cataracts, diabetic retinopathy, and hypertensive retinopathy). Some conditions (neurological disease, impaired depth perception or eye disease, dizziness, and other medical conditions) were not evaluated as potential risk factors for subsequent major long-bone fractures if they were treated and well controlled before the fracture. The causes of fracture were categorized as falls from a standing height or less or ambulation during nursing care.

All radiographic diagnoses were confirmed by an orthopedist and a radiologist. Fractures were classified as hip fractures (intertrochanteric or femoral neck) or major long-bone fractures (humerus, radius, ulna, femur, or tibia).

Statistical Analysis

Differences in quantitative data between the groups were analyzed with Student's *t*-test (for normally distributed data) or the Mann-Whitney *U*-test (for nonnormally distributed data), and differences in qualitative data between the groups were analyzed with the chi-square test. Differences in mortality rates between the groups were analyzed with the chi-square test. The effect of each predisposing risk factor on the rate of subsequent major long-bone fractures was assessed with univariate and multivariate analyses. Potential risk factors that showed a significant relationship with subsequent fracture on univariate analysis were included in the multivariate models. The results were adjusted for age and sex and expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Hazard ratios were calculated with the Cox regression model with multivariate analysis. A *p*-value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

The demographic data and clinical features of each group are summarized in **Table 1**. The group

Hip and Long Bone Fractures and Survival

Table 1 Demographic characteristics and clinical features of patients with hip fracture with or without subsequent major long-bone fractures

	Subsequent fracture (n=71)		No subsequent fracture (n=773)		p-value
	n	%	n	%	
Age group (years)					
55-74	50	70.4	212	27.4	0.001#
75-84	20	28.2	350	45.3	
>85	1	1.4	211	27.3	
Sex					
Male	33	46.5	76	9.8	0.001#
Female	38	53.5	697	90.2	
Cause of hip fracture/subsequent fracture*					
Fall from a standing position	71/70	100/98.6	770/-	99.6/-	0.925**
Ambulation during nursing care	0/1	0/1.4	3/-	0.4/-	
Mobility before hip fracture					
Community, household without gait aid	70	97.1	761	98.4	0.599
Household with gait aid/wheelchair, bedridden	1	2.9	12	1.6	
Time to subsequent fracture					
≤12 months	52	73.3	-	-	-
12-48 months	2	2.8	-	-	
>48 months	17	23.9	-	-	

$p < 0.05$ was considered to be significant. *refers to the number of patients in whom the initial hip fracture/subsequent fracture resulted from the cause listed. **indicates a nonsignificant difference between the groups with and without subsequent fracture (a comparison in terms of the initial hip fracture episode).

with subsequent long-bone fractures had a higher percentage of patients aged <75 years at the time of the first hip fracture (OR: 6.3, 95% CI: 3.7-10.7, $p = 0.001$) and a higher proportion of males (OR: 7.96, 95% CI: 4.7-13.4, $p = 0.001$) than did the group without subsequent fractures (**Table 1**).

There were no significant differences between the groups with respect to fracture causes or prefracture mobility (**Table 1**). Subsequent fractures occurred most commonly 0 to 12 months after the first hip fracture (73.3% of subsequent fractures occurred during this time) (**Table 1**). Patients without subsequent fractures were significantly more likely to have hypertension, knee osteoarthritis, heart disease, respiratory disease, neurological disease, or renal disease ($p < 0.05$ for all) (**Table 2**). Multivariate analysis showed that age <75 years and male sex were independent risk factors for subsequent fractures of major long bones (**Table 3**).

The mortality rates during the first year and from 1 to 5 years after the most recent fracture were 5.6% and 1.4%, respectively, in the group with

subsequent fractures and 4.7% and 1.4%, respectively, in the group without subsequent fractures (**Table 4**). These results indicate that patients with subsequent fractures did not have significantly higher mortality rates or significantly shorter survival times than did patients without subsequent fractures during the first year ($p = 0.71$) or from 1 to 5 years after the most recent fracture ($p = 0.99$). There was also no significant difference in the overall mortality rate between the group with subsequent fractures (including subgroups with subsequent upper-extremity or lower-extremity fractures) and the group without subsequent fractures ($p = 0.937$). Age- and sex-adjusted analysis with the Cox proportional hazards regression model and multivariate analysis showed that there was no significance difference in survival between groups with or without subsequent long-bone fractures (hazard ratio: 1.25, 95% CI: 0.49-3.23, $p = 0.64$) (**Fig. 2**).

The most frequent site of subsequent long-bone fracture was the distal radius (51%), followed by the proximal humerus (25%), tibia (21%), and supracondylar area of the femur (3%).

Table 2 Medical co-morbidities in hip fracture patients with or without subsequent major long bone fractures

	Subsequent fracture (n=71)		No subsequent fracture (n=773)		<i>p</i> -value
	n	%	n	%	
Heart disease	7	9.9	222	28.7	0.001#
Respiratory disease	3	4.2	141	18.2	0.001#
Hypertension	34	47.9	625	80.9	0.001#
Diabetes mellitus	18	25.4	282	36.5	0.061
Renal disease	2	2.8	116	15.0	0.001#
Eye disease	5	7.0	114	14.7	0.08
Neurological disease	3	4.2	153	19.8	0.04#
Knee osteoarthritis	1	1.4	133	17.2	0.008#

#*p*<0.05 was considered to be significant.

Table 3 Multivariate analyses of factors associated with subsequent major long bone fractures

	Adjusted odds ratio	95% confidence interval	<i>p</i> -value
Male gender	9.75	5.4-17.4	0.001#
Age <75 year at first hip fracture	7.5	4.2-13.4	0.001#

#*p*<0.05 was considered to be significant.

Table 4 Mortality rates of hip fracture patients with or without subsequent major long bone fractures

	Subsequent fracture (n=71)		No subsequent fracture (n=773)		<i>p</i> -value#
	n	%	n	%	
Mortality during first year	4	5.6	36	4.7	0.71
Mortality between 1 and 5 years	1	1.4	11	1.4	0.99

#*p*<0.05 was considered to be significant.

The most frequent cause of death in the group with subsequent fractures was sepsis of unknown cause (60%), followed by respiratory failure due to pneumonia (20%) and sepsis due to urinary tract infection (20%). The most frequent cause of death in the group without subsequent fractures was sepsis of unknown cause (34%), followed by respiratory failure due to pneumonia (30%), heart disease (acute coronary syndrome, heart failure) (17%), sepsis due to urinary tract infection (11%), neurological disease (cerebral infarction, intracerebral hemorrhage) (6%), and sepsis due to surgical site infection (2%). The major causes of death in both groups were pneumonia and sepsis due to urinary tract infection or unknown. Heart disease and other diseases were less common causes of death. However, there was

no significant difference in the prevalence of mortality causes between the groups (*p*=0.314).

Discussion

The present study evaluated patients who had a first hip fracture and then had or did not have a subsequent major long-bone fracture. There have been no major changes in the management of hip fractures at our center over the last 8 years. This study evaluated the survival times of patients who survived to hospital discharge and returned to life in the community. We found that the survival times of patients with subsequent fractures were not significantly shorter than those without subsequent fractures.

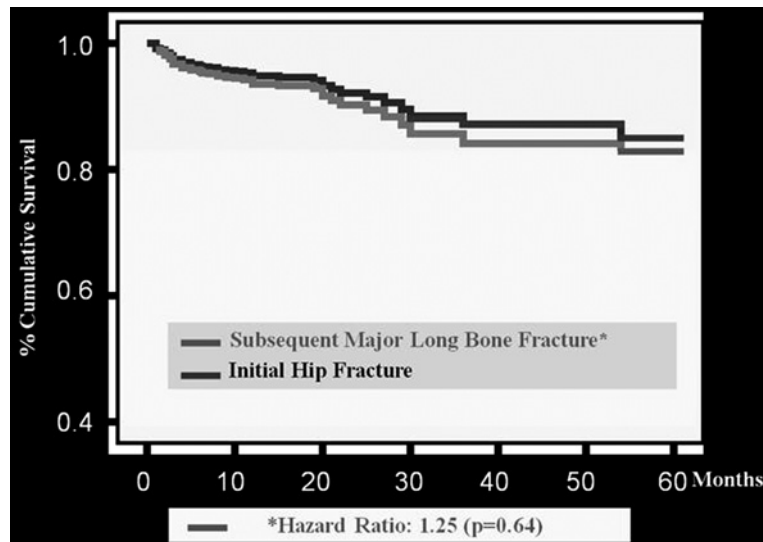


Fig. 2 Survival curve analysis for patients with or without major long-bone fractures after hip fractures. The relationship between cumulative survival ratio and follow-up period (months) is shown for each group. The hazard ratio for patients with subsequent fractures was insignificant.

In the present study, we examined the survival time of patients living in the community³ who had hip fractures and then had or did not have subsequent major long-bone fractures. Colón-Emeric et al.³ have also studied the survival of community dwelling men and male veterans with hip fracture and subsequent fractures. To determine survival in their study population, they excluded in-hospital deaths from their analysis but included all subsequent fractures, including those of the hip, pelvis, extremities, and vertebrae. In addition, Berry et al.² found that the mortality rate is highest immediately after fracture surgery and that better postoperative predictors of mortality are required to discriminate between patients at immediate risk (high risk) of in-hospital death and those likely to survive to discharge. On the basis of previous studies, we decided to exclude patients who died in hospital shortly after admission or who died of causes unrelated to fracture. Therefore, these patients would not confound the results of survival in our study. This method primarily represents the survival of patients who were discharged or who were older adults living in the community³. To the best of our knowledge, the present study is one of few evaluating the survival of community-based individuals after a first hip fracture and focusing on

the effects of subsequent major long-bone fractures. This information is useful for the management of elderly patients with fractures.

The present study found that community-based individuals who had sustained a first hip fracture and then sustained a subsequent major long-bone fracture had a shorter survival time than those who did not have a subsequent fracture, but this difference was not significant. These results may be explained by the smaller numbers of elderly patients and patients with comorbidities who sustained major long-bone fractures. The larger numbers of patients with comorbidities in the group without subsequent fractures might have affected the mortality rates in that group⁴. The differences in survival times between the groups might, therefore, be unrelated to the fractures. The lack of significant differences in survival times and hazard ratios between the groups might also be explained by the 5-year follow-up period. Differences between groups might become significant with a longer follow-up period. In addition, even if sex ratios and means ages differed between the groups in this study, the age- and sex-adjusted analysis⁵ with the Cox proportional hazards regression model and multivariate analysis was performed which could control for confounding and increase the efficiency of results of this study.

However, further studies with more specific gender- and age-matched control groups and longer follow-up times should be performed to determine the survival times of patients with hip fracture who have or do not have subsequent fractures.

The risk factors for a first hip fracture have been extensively studied^{6,7}. Various risk factors for second hip fractures have also been reported⁸⁻¹⁴. However, few studies have reported on risk factors for major long-bone fractures after a first hip fracture. A meta-analysis by Kanis et al has found that the relative risk of fractures is increased after a first fracture¹⁵. Several previous studies have investigated the risks of subsequent fractures after an initial fracture of an extremity or vertebra¹⁶⁻¹⁹. Center et al have reported on risk factors for subsequent fracture after initial low-trauma fractures, including fractures of the hip, vertebra, pelvis, distal femur, proximal tibia, multiple ribs, and proximal humerus, and all minor osteoporotic fractures with the exception of fractures of the fingers and toes²⁰. Colón-Emeric et al have also studied the risk factors for subsequent fractures, including fractures of the hip, pelvis, extremities, and vertebrae, after a first hip fracture³. These previous studies had different settings from our study. We focused on major long-bone fractures that occurred after first hip fractures in community-based individuals. Berry et al. have reported the risk of subsequent fractures after a first hip fracture²¹. They studied residents of nursing homes and included second hip fractures in their subsequent-fracture group; the risks of subsequent fractures might, therefore, have differed between their study and our study. Our results indicate that male sex is a risk factor for a subsequent major long-bone fracture. Men tend to be more physically active after a hip fracture than women and, therefore, have more opportunity to sustain a subsequent fracture. Age <75 years at the time of hip fracture was also a risk factor for a subsequent major long-bone fracture. This relation may be explained by higher mobility and function in this age group and a better physical recovery after hip fracture^{2,22}. Younger male patients might be able to maintain higher activity levels after a fracture and then, as a result, be more likely to sustain an extremity fracture. Our results

are consistent with those of a previous study that found that older patients and female patients were not at increased risk for subsequent fractures²¹. Our results also indicate that patients without subsequent fractures had more comorbidities than did patients with subsequent fractures. These comorbidities might limit activity levels and thereby reduce the likelihood of subsequent fractures. Patients with higher numbers of comorbidities might be low functioning with limited activity and, consequently, be at lower risk of subsequent falls and fractures²¹.

The 2 most common major long bones fractured were the radius and humerus. This finding might be explained by elderly patients tending to respond to falling and tripping by using their upper extremities for protection²³. Even if our study showed that subsequent major long-bone fractures have only a minor effect on survival, Robinson et al²⁴ have shown that such fractures have negative effects on patients' lives, such as higher healthcare costs. Therefore, the risks of subsequent fractures should be addressed in all patients with hip fractures and should be reduced where possible with education regarding fracture prevention and regular rehabilitation programs. For example, if physicians have patients with initial hip fractures who are at increased risk for subsequent fracture, they should provide a protocol to decrease that risk. Efforts should be made to decrease the rate of subsequent major fractures of long bone and their associated burdens, such as higher healthcare costs. In addition, we found that the incidence of subsequent major long-bone fractures was highest during the first year after hip fracture. These results regarding the nature and consequences of subsequent fractures suggest that prevention requires a multidisciplinary approach. Regular rehabilitation programs might be useful for all patients, especially during the first year after hip fracture.

The most common causes of death in patients with and without long-bone fractures after hip fracture were pneumonia and sepsis, which might be due to decreased mobility or being bedridden. These results were similar to those of a previous study showing an increased risk of death from infection,

particularly within 12 months of a hip fracture²⁵.

Conclusions

This study found that the survival times after the most recent fracture does not differ significantly between hip fracture patients with subsequent major long bone fractures and those without. All patients with hip fracture should receive the same holistic care. The risks of subsequent fracture should be addressed in all patients with hip fracture and should be reduced where possible with education regarding fracture prevention and regular rehabilitation programs. Efforts should be made to decrease the rates of subsequent major long-bone fractures and their burdens, even if such fractures have only a minor effect on survival in community-dwelling individuals.

References

- Cooper C, Campion G, Melton LJ 3rd: Hip fractures in the elderly: A world-wide projection. *Osteoporosis Int* 1992; 2: 285–289.
- Berry SD, Samelson EJ, Hannan MT, et al.: Second Hip Fracture in Older Men and Women: The Framingham Study. *Arch Intern Med* 2007; 167: 1971–1976.
- Colón-Emeric CS, Sloane R, Hawkes WG, et al.: The Risk of Subsequent Fractures in Community dwelling Men and Male Veterans with Hip Fracture. *Am J Med* 2000; 109: 324–326.
- Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ 3rd: Population-based study of survival after osteoporotic fractures. *Am J Epidemiol* 1993; 137: 1001–1005.
- Faresjö T, Faresjö A: To Match or Not to Match in Epidemiological Studies—Same Outcome but Less Power. *Int J Environ Res Public Health* 2010; 7: 325–332.
- Cummings SR, Nevitt MC, Browner WS, et al.: Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995; 332: 767–773.
- Dargent-Molina P, Favier F, Grandjean H, et al.: Fall-related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet* 1996; 348: 145–149.
- Angthong C, Suntharapa T, Harnroongroj T: Major risk factors for the second contralateral hip fracture in the elderly. *Acta Orthop Traumatol Turc* 2009; 43: 193–198.
- Chapurlat RD, Bauer DC, Nevitt M, Stone K, Cummings SR: Incidence and risk factors for a second hip fracture in elderly women. The Study of Osteoporotic Fractures. *Osteoporos Int* 2003; 14: 130–136.
- Dretakis KE, Dretakis EK, Papakitsou EF, Psarakis S, Steriopoulos K: Possible predisposing factors for the second hip fracture. *Calcif Tissue Int* 1998; 62: 366–369.
- Egan M, Jaglal S, Byrne K, Wells J, Stolee P: Factors associated with a second hip fracture: a systematic review. *Clin Rehabil* 2008; 22: 272–282.
- Mitani S, Shimizu M, Abo M, Hagino H, Kurozawa Y: Risk factors for second hip fractures among elderly patients. *J Orthop Sci* 2010; 15: 192–197.
- Saxena P, Shankar J: Contralateral hip fractures - can predisposing factors be determined? *Injury* 2000; 31: 421–424.
- Yamanashi A, Yamazaki K, Kanamori M, et al.: Assessment of risk factors for second hip fractures in Japanese elderly. *Osteoporos Int* 2005; 16: 1239–1246.
- Kanis JA, Johnell O, De Laet C, et al.: A metaanalysis of previous fracture and subsequent fracture risk. *Bone* 2004; 35: 375–382.
- Cuddihy MT, Gabriel SE, Crowson CS, O'Fallon WM, Melton LJ 3rd: Forearm fractures as predictors of subsequent osteoporotic fractures. *Osteoporos Int* 1999; 9: 469–475.
- Haentjens P, Johnell O, Kanis JA, et al.: Evidence from data searches and life-table analyses for gender-related differences in absolute risk of hip fracture after colles' or spine fracture: Colles' fracture as an early and sensitive marker of skeletal fragility in white men. *J Bone Miner Res* 2004; 19: 1933–1944.
- Johnell O, Kanis JA, Oden A, et al.: Fracture risk following an osteoporotic fracture. *Osteoporos Int* 2004; 15: 175–179.
- Lauritzen JB, Lund B: Risk of hip fracture after osteoporosis fractures: 451 women with fracture of lumbar spine, olecranon, knee or ankle. *Acta Orthop Scand* 1993; 64: 297–300.
- Center JR, Bliuc D, Nguyen TV, Eisman JA: Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA* 2007; 297: 387–394.
- Berry SD, Samelson EJ, Ngo L, Bordes M, Broe KE, Kiel DP: Subsequent Fracture in Nursing Home Residents with a Hip Fracture: A Competing Risks Approach. *J Am Geriatr Soc* 2008; 56: 1887–1892.
- Mossey JM, Mutran E, Knott K, Craik R: Determinants of recovery 12 months after hip fracture: the importance of psychosocial factors. *Am J Public Health* 1989; 79: 279–286.
- Senden R, Savelberg HHCM, Adam JJ, Grimm B, Heyligers IC, Meijer K: Differences in trip recovery between young and elderly subjects. Proceedings in the Summit of European Orthopaedic Research Society. 30 June - 2 July 2010, Davos, Switzerland.
- Robinson PM, Harrison T, Cook A, Parker MJ: Orthopaedic injuries associated with hip fractures in those aged over 60 years: A study of patterns of injury and outcomes for 1971 patients. *Injury* 2012; Mar 30. [Epub ahead of print].
- Wehren LE, Hawkes WG, Orwig DL, Hebel JR, Zimmerman SI, Magaziner J: Gender differences in mortality after hip fracture: the role of infection. *J Bone Miner Res* 2003; 18: 2231–2237.

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