Mortality and osteoporotic fractures: is the link causal, and is it modifiable?

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ABSTRACT

Osteoporosis is a global problem with an expected increase in fracture prevalence and public health burden as the world's population ages. Although excess mortality is well-described in those with low bone mineral density as well as those with recent hip and vertebral fractures, some uncertainty remains about whether this link is causal. Survival depends greatly on the fracture types, age, gender, and race. Deaths are predominately due to comorbidities, but may also be attributed to the fracture event itself, either directly or indirectly. The goal of osteoporosis care is prevention of fractures and ultimately reduction in morbidity and mortality. Until recently, there have been no data showing that osteoporosis treatment improves mortality, and even now the extent of these data are rather limited. Large observational cohort studies over considerable time are needed to determine whether improving osteoporosis quality of care will improve mortality rates.

Introduction

Osteoporosis is a systemic skeletal disorder characterized by reduced bone strength predisposing to an increased risk of fracture. The clinical and public health importance of osteoporosis arises primarily from fragility fractures. Fragility fractures are one of the most common causes of disability and a major contributor to costs of medical care in all regions of the world (1). Clinical consequences of fracture include short and long-term morbidity characterized by pain, limitation of function, decreased health-related quality of life, and increased mortality. As fracture prevalence increases in tandem with increasing longevity of the population, osteoporosis is becoming an even more significant public health burden (2-7).

The mortality risk of patients with osteoporosis is increased by approximately 1.5-fold for each standard deviation decrease in bone mineral density (BMD) (8-10). Survival estimates are dependent on fracture location and the completeness and duration of follow-up after fractures. Excess mortality in osteoporotic fractures occurs following fractures of the spine (radiographic and clinical fractures) (11-23) and particularly of the hip (17, 24-36) . By contrast, there appears to be no excess mortality among patients who sustain a distal forearm, foot, or ankle fracture (12, 14, 17, 37). Although mortality rates are lower in younger elderly individuals who sustain fractures, people in this age group constitute a large proportion of the elderly population, and thus contribute substantially to the total number of excess deaths due to osteoporosis (13).

While osteoporosis-associated mortality is a well-recognized public health concern, the impact of other risk factors on mortality associated with osteoporosis remains unclear. Osteoporosis treatment has been shown to reduce the risk of subsequent fracture, but the impact on mortality has been minimally studied (38, 39). Understanding the possible relationship between mortality and osteoporosis fractures is needed to design strategies to improve quality of care in osteoporosis.

Mortality outcomes of osteoporosis have been analyzed in cohort studies and case-control observational study designs (often using linked hospital and death data). Many of these studies examine the observed mortality compared with the *expected* mortality of the (healthier) general population (13, 40, 41) of same sex and age; the difference between the observed and expected represents excess mortality. The cause of death is not always noted, and even if described, the contribution of fractures or falls may be underestimated since only the most proximate cause of death and not the inciting event is usually reported (42).

In cohort studies, the relationship between fracture (the exposure) and mortality (the outcome) is evaluated after adjusting for a variety of potentially confounding factors. Since people who fracture have generally poorer general health and physical function, earlier death may be a result of the patients' poor health, greater number of pre-fracture comorbidities, and poor physical function. For some people, a fracture may be a sentinel event that leads to new diseases, difficulty with rehabilitation, progressive functional decline, loss of independence, and disability. Thus related health states, not directly caused by the fracture event itself, may be as important as the fracture in premature mortality. In order to delineate the quantum of excess mortality contributed by osteoporotic fractures and the extent to which mortality may be reduced through fracture prevention, control groups in these studies should ideally be subjects with health states as similar as possible to those of the study population. In addition to patient factors, the process of care, including surgery, rehabilitation, and post-care disposition, are crucial to quantify in order to determine which factors, if any, predispose to better post-fracture outcomes.

This article reviews the recent clinical and epidemiological characteristics of mortality associated with osteoporotic hip and vertebral fractures worldwide.

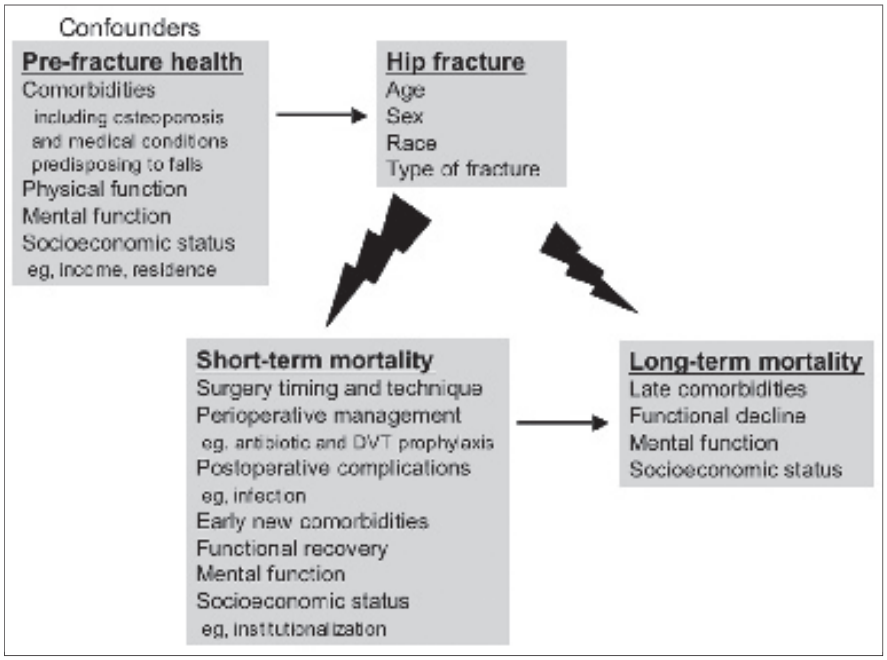

Fig. 1. Predictors of mortality following osteoporotic hip fractures.

Hip fractures and mortality

Hip fractures are the most serious of all osteoporotic fractures with extremely costly consequences. While mortality rate is undoubtedly high following hip fracture, there is still considerable controversy over the direct contribution of hip fractures to this excess mortality. Hip fracture may result in mortality either directly, indirectly, mediated through new or altered comorbidities, or as a result of pre-existing comorbidities that are simply associated with fracture risk. The first three circumstances represent causal (or partially causal) associations, whereas the latter would represent an example of a confounding factor (Fig. 1).

Mortality rates are highest during the first 6 months immediately after the fracture; lower, but still greater than in the general population, for up to 12 months post-fracture (25, 26, 34-36, 43-45); and appear to decrease with time thereafter. Mortality rates range from 10% to 45% in the first year (Table I). When and whether the mortality curves converge with those of the general population varies in different studies. The majority of studies show persistently increased mortality rates (12, 17, 25, 26, 32, 35, 40, 43, 44, 46), while others suggest no long-term elevated mortality over time (34, 47) relative to that expected in older individuals. Differences across studies may be explained in part by variations in cohort characteristics (age, institutionalized, etc), health of the comparator groups, method of calculating excess mortality, and whether frailty before fracture has been taken into account adequately.

In a recent Danish population-based cohort of *all* patients with hip fractures, the mortality rate was nearly 30% compared with age- and gender matched subjects from the general population. Mortality in patients was 19% greater than in the control subjects (relative survival = 0.81) in the first year after fracture. The major causes of death were factors associated with the accident leading to the fracture, accounting for 71% of all deaths within the first 30 days. Little of the excess mortality was attributed to pre-morbid conditions, with the exception of lower income. There was a small but constant 1.8% excess annual mortality for the subsequent 19 years. Therefore, over a period of 20 years, the long-term excess mortality contributed more than the short-term excess (35). In contrast, Tosteson *et al*. found no evidence of excess mortality beyond 6 months following hip fracture, despite adjustments for various pre-morbid conditions and function, in an elderly U.S. population that included persons who were institutionalized (34).

Risk factors associated with hip fracture mortality

Sex, age and race/ethnicity

Although the prevalence of hip fractures is higher in women, men have a higher risk of death than women after a hip fracture (28, 29, 32, 35, 41, 43, 48), but the gender-based difference is not significant after adjustment for age (17). The proportion of years of life lost was higher in men, even after considering higher mortality rates of males in the general population (41).

Intuitively, age is an independent predictor of mortality. However, some studies have shown an inverse relationship between age and excess risk

Table I. Studies on hip fractures (HFx) and mortality rates and ratios (past 5 years).

Study (ref)	Location	Number of patients	Deaths in patients with HFx	Relative risk compared with non-fractured (95% CI)	Mortality rate by year after HF (% or per 100 person-years (95% CI))			Standardized mortality ratio (95% CI)		
					<1 year	1 to <5 years	≥5 years	<1 year	1 to <5 years	≥5 years
Hindmarsh 2008 (28)	New South Wales, Australia	16836 HFx 65 -74 yo M 65 -74 yo W 85+ yo M 85+ yo W				18 10 35 20		1.2* 1.1* 1.6* 1.3*	1.3* 1.1* 1.8* 1.4*	
Paksima 2008 (32)	United States (single hospital)	1050 HFx	479		2.7 in-hospital	12.9 (1y) 18.5 (2y)	41.2 (5y) 75.3 (10y)		1.5 (1y) 1.1 (2y) 1.0 (3y)	0.9 (5y) 0.6 (10y)
Vestergaard 2007 (35)	Denmark	169145 HFx 524010 controls	121953	2.3 (2.2–2.3) [a]2.0 (1.9–2.0)		28*		2*	1.3*	1.2*
Tosteson 2007 (34)	United States	25178 730 incident HFx	292	< 6 months [b]11.6 (8.9–15.1) [c]6.3 (4.8–8.2) [d]6.3 (4.8–8.2) > 6 months [b] 1.4 (1.2–1.6) [c] 1.0 (0.9–1.2) [d]1.0 (0.9–1.2)	20					
Muraki 2006 (31)	Japan	480 HFx			3.5 in-hospital	11.5 (1 y)	59* (5y) 82* (10y)			
Vidal 2006 (36)	Brazil	606 post hip repair	130		/100 py 95 (1mo) 44 (1–3mo) 11 (3mo–1y)			1.1 (7.9–1.5) 5.1 (3.7–7.0)	1.4 (1.0–1.8)	
Pande 2006 (33)	United Kingdom	100 M HFx 100 controls		[g] 6.7 (3.4–13.4) [g]6.2 (3.1–12.4) [g] 7.2 (3.5–14.7)	25 (3mo)	45 (1y) 63 (2y)				
Karagiannis 2006 (29)	Greece (single hospital)	499 HFx post surgery				IT: FN 17.9: 11.3 ns	IT: FN 48.8: 34.7 (5y) 76: 58 (10y)			
Farahmand 2005 (26)	Sweden	2245 W HFx 4035 W controls	896	2.3 (2.0–2.5)	4.3 (3mo)	10.6 (1y)	[e]53 [f]16			
Franzo A, 2005 (27)	Italy	6629			20.0	25.3				
Alegre-Lopez J, 2005 (24)	Spain	218	49		65.3 (3mo)	21 (1y)				
Johnell 2004 (47)	Malmö, Sweden	1143	678		22.3					

HFx: Hip fracture; M: men; W: women; ns: not significant; yo: years old; mo: months; y: year; /100 py: per hundred person-years; IT: intertrochanteric fracture; FN: femoral neck fracture; *derived from graph; a: adjusted for multiple covariates; b: adjusted for age, sex and race; c: adjusted for age, sex, race, functional status, comorbid conditions and socioeconomic variables; d: adjusted for age, sex, race, functional status, and comorbid conditions; e: previous serious hospitalization; f: without previous serious hospitalization; g: adjusted for age and quality of life measures.

Table II. Factors related to mortality following hip fracture (relative risk ratio (95% CI)) (Variables refer to those before fracture unless otherwise stated).

Study	Paksima 2008 (32)	Vestergaard 2007 (35)	Muraki 2006 (31)	Karagiannis 2006 (29)		Farahmand 2005 (26)		Franzo 2005 (27)	Alegre-Lopez 2005 (24)
				5 years	10 years	≤1 year	>1 year		
Sociodemographic and fall risk factors									
Men	1.4 (1.2–1.7)	1.3 (1.3–1.4)	1.4 (1.1–2.0)	1.8 (1.3–2.4)	1.7 (1.2–2.0)			2.4 (2.1–2.8)	2.4 (1.0–6.0)
Age	1.0 (1.0–1.1)	[a] 2.8 (2.8–2.9) [b] 6.3 (6.2–6.4) [c] 12.7 (12.5–12.9)	1.0 (1.0–1.0)	1.09 (1.1–1.1)	1.1 (1.1–1.1)	[d] 8.4 (2.5–28.0) [e] 3.7 (2.2–6.3) [f] 2.1 (1.5–2.8)	[d] 2.3 (1.3–3.9) [e] 1.5 (1.1–2.1) [f] 1.6 (1.3–2.1)	1.6 (1.5–1.7)	1.2 (0.3–4.2) (≥80y)
Body mass index<22 22–25 >25			ns				1.9 (1.4–2.6) 1.6 (1.2–2.2) 1.5 (1.1–2.1)		
Smoking							[g] 1.6 (1.2–2.0) [h] 2.0 (1.4–3.0) [i] 1.9 (1.3–2.7)		
Use of hormone replacement therapy							1.7 (1.4–2.1) (never) 1.7 (1.2–2.4) (ever)		
Living single		1.1 (1.1–1.1)							1.5 (0.4–5.6)
Income		1.5 (1.5–1.6)							
Institutionalized at discharge			ns						2.9 (1.0-8.4)
Comorbidities and Physical Function									
Charlson Index 0 1–2 3–4 >4		Referent 1.8(1.8–1.8) 2.7 (2.6–2.7) 4.1 (4.0–4.2)						2.2 (2.0–2.4) (Charlson index ≥ 1)	0.6 (0.1–3.5) (Comorbidity ≥ 1)
High ASA score at fracture	1.5 (1.2–1.8)								
Without previous hospitalization With previous hospitalization							1.7 (1.4–2.2) 1.7 (1.3–2.2)		
No. of hospitalization before index date 1 2–5 >5							1.4 (0.9–2.2) 1.6 (1.1 (2.4) 3.4 (1.5–7.8)		
Diabetes mellitus			1.5 (1.1–2.0)						

Study	Paksima 2008 (32)	Vestergaard 2007 (35)	Muraki 2006 (31)	Karagiannis 2006 (29)		Farahmand 2005 (26)		Franzo 2005 (27)	Alegre-Lopez 2005 (24)
				5 years	10 years	≤1 year	>1 year	1 year	
COPD	1.3 (0.9–1.7)		1.0 (0.6–2.0)						
Heart failure	1.4 (1.0–1.9)		1.1 (0.8–1.7)	1.9 (1.3–2.7)	1.7 (1.2–2.3)				
Cancer	19 (12–31)								
Alcoholism	2.2 (1.7–2.9)	1.7 (1.7-1.8)					[j] 1.7 (1.3 (2.2) [k] 2.3 (1.6–3.2)		
Gastrectomy/colectomy			2.2 (1.4–3.5)						
Ambulatory status	1.3 (1.0–1.6) (assistive device)		[n] 1.7 (1.0–2.6) [o] 1.7 (1.2–2.3) [p] 1.8 (1.1–2.9)				[l] 1.4 (1.1–1.8) [m] 2.1 (1.6–2.8)		4.4 (1.3–14.4) (limited function)
Mental Function									
Poor mental status			1.5 (1.2–2.0) (dementia)						7.0 (1.7–28)
Delirium									0.6 (0.2–1.5)
Surgical and perioperative factors									
High surgical volume								1.2 (1.1–1. 3)	
IT fracture FN fracture			1.5 (1.1–1.9) Referent	1.3 (0.9–1.9)* Referent	1.4 (1.0–1.8)* Referent	2.4 (2.0–2.6) 2.2 (1.9–2.6)			Referent 0.6 (0.3–1.3)
Time to surgery ≥2 days								1.1 (1.0–1.2)	
Year of fracture								0.9 (0.9–1.0)	
Major postoperative complication	1.9 (1.4–2.6)		2.0 (1.1–3.6) (pneumonia)						
Number of operations ≥ 1								2.8 (2.1–3.7)	

95% CI: 95% Confidence Interval; ASA, American Society of Anesthesiologists; COPD: chronic obstructive pulmonary disease; y: years; ns: not significant; IT: intertrochanteric fracture; FN: femoral neck fracture; a: 65-74 years old; b: 75-84 years old; c: ≥ 85 years old with <65 years old as reference; d: <70 years old; e: 70-75 years old; f: ≥ 76 years old; g: never smoked; h: former smoker; i: current smoker; j: no alcohol; k: yes alcohol; l: leisure physical activity <1 h/week; m: leisure physical activity ≥1 h/week; n: walk with walker; o: walk with support; p: non-ambulatory.

Table III. Studies on vertebral fractures (VF) and mortality rates and ratios.

Study	Location	Number of patients	Deaths in patients with VF	Relative risk of death compared with non-fractured (95% CI)	Mortality rate by year after VF (% or per 100 person-years) (95% CI)			Standardized mortality ratio (95% CI)		
					<1 year	1 to <5 years	≥5 years	<1 year	1 to <5 years	≥5 years
Clinical VF										
Lau 2008 (85)	United States	97142 VF 428956 controls	39707	[j]1.8 (1.8–1.9)		46.1 (3y)	69.1 (5y) 89.5 (7y)			
Bouza 2007 (11)	Spain	7100 Osteoporotic VF By ICD-9 code	246 in-hospital		3.5 in-hospital					
Kanis 2004 (20)	Sweden	16051 (40358 py) By ICD-9 codes	M1597 W4065		/100py	/100py	/100py			
		M 50 yo			3.2 (2.8–3.7)	1.8 (1.6–2.0)		13.2	7.3	
		M 80 yo			15.9 (15.2–16.5)	8.8 (8.4–9.2)		2.2	1.2	
		W 50 yo			1.9 (1.4–2.7)	1.6 (1.1–2.2)		12.5	10.2	
		W 80 yo			12.9 (11.3–14.9)	10.9 (9.2–12.1)	15* (5y) 20* (8y)	2.9	2.4	
Cauley 2000 (12)	United States (FIT)	6459 W 2027 prevalent VF 119 incident VF	11	[b]8.6 (4.5–16.7)		/100py 6.8				
Center 1999 (13)	Dubbo, Australia	4312 subjects			/100py	/100py	/100py			Incident / Prevalent
		76 W incident VF	16		13.5	1.6	1.1			1·6 (1·4–1·8) / 1·8 (1·6–2·1)
		38 M incident VF	17		42	4.8	1.4			1·8 (1·6–2·0) / 3·7 (3·4–3·9)
										1.7 (1.5–1.8)
										2.4 (2.2–2.6)
Cooper 1993 (14)	Rochester, Minnesota United States	335 incident VF	76				39 (5y)			1.2 (1.1–1.4)
Radiographic morphometric VF										
Trone 2007 (22)	United States	1580 subjects 178 prevalent VF	73	1 VF: 1.1 (0.8–1.4) ≥2 VF: 1.6 (1.0–2.4)			41 (8y)			1.5 (p<0.001)

Study	Location	Number of patients	Deaths in patients with VF	Relative risk of death compared with non-fractured (95% CI)	Mortality rate by year after VF (% or per 100 person-years) (95% CI)			Standardized mortality ratio (95% CI)		
					<1 year	1 to <5 years	≥5 years	<1 year	1 to <5 years	≥5 years
Hasserius 2005 (82)	Sweden (EVOS)	257 prevalent clinical VF 23 incident VF (over 1st 12y)	64M, 166W	M: not verifiable W: 2.8 (1.0-7.9) Incident VF			/100py 11.2 9.5 (22y)			1.5* 1.5* (22y)
Naves 2003 (21)	Spain Part of EVOS	308 M 316 W 147 prevalent VF 11 incident VF	65M 37W	M:[c] not increased W: [d] 2.2(1.1–4.6) [f] 2.0 (1.0–4.1) Post all VF			7* (5y) 6* (5y) 25* (8y) 22* (8y)			1.3* (5y) 2.2* (5y) 1.6* (8y) 3.1* (8y)
Kado 2003 (19)	United States (part of SOF)	7233 1414 prevalent VF 389 incident VF		1.3 (1.1–1.6) [a] 1.1 (0.9–1.3) Incident VF			[g] 27* (8y) [h] 35* (8y)			
Jalava 2003 (16)	Finland	677 352 prevalent VF 118 incident VF	31 7	Prevalent VF: 4.4 (1.9–10.6); [a] 2.4 (0.9–6.2) Incident VF: No increase		/100py ≤ 59 yo: 2.1 ≥ 69 yo: 3.2				
Ensrud 2000 (23)	United States (FIT)	6459 W 2027 ≥1 prevalent VF		1.6 (1.1–2.3) [a] 1.5 (1.1–2.2)						
Kado 1999 (18)	United States (SOF)	9575 W 1915 with ≥1 prevalent VF		1.2 (1.1–1.4)			[i] 2.3, 2.5, 2, 9, 3.2, 4.4 /100py (8y)			
Ismail 1998 (15)	Europe (EPOS)	6480 subjects 438 M prevalent VF 429 W prevalent VF		M 1.3(0.9-2.0); [a] 1.2 (0.7–1.8) W1.9 (1.0–3.4); [a] 1.6 (0.9–3.0)		M 1.4* (1y) M 2.4* (4y) W1.1* (1y) W2.6* (4y)				

VF: vertebral fracture; M: men; W: women; yo: years-old; 95% CI: 95% Confidence Interval; ; EVOS: European Vertebral Osteoporosis Study; FIT: Fracture Intervention Trial (alendronate *vs*. placebo); SOF: Study of Osteoporotic Fractures; EPOS: European Prospective Osteoporosis Study; *derived from graph; a: adjusted for multiple covariates ; b: adjusted for age, study group and treatment assignment; c: by any radiographic criteria; d: McCloskey-Kanis radiographic criterion; f: Genant Grade II radiograghic criterion; g: no prevalent and ≥1 incident VF; prevalent and ≥1 incident VF; i: for 1, 2, 3, 4, ≥5 prevalent VF respectively; j: adjusted for comorbidity; yo: years old; mo: months; y: years; /100 py: per hundred person-years.

of death. Older hip fracture patients have a much lower excess or relative risk of mortality than younger patients (i.e., age was an effect modifier) (26, 28, 35), since more older people in the general population die. In people with diseases, relative risk is almost always higher in younger subjects while absolute risk is higher in older subjects, as younger (control) people who do not have diseases are less likely to die.

Although understudied, there also appears to be a race/ethnicity disparity in mortality after hip fractures. Using a Medicare claims database, black women had higher mortality after a hip fracture than white women. The survival curves for black women and white women diverged during the first 9 months following hip fracture, thereafter remaining parallel. Men experienced the highest mortality, with nearly identical rates among blacks and whites. The observed race/ethnicity differences in fracture mortality were consistent despite stratification by age at time of hip fracture and by number of comorbid medical conditions (49). By contrast, early or late mortality following hip fracture was not affected by black versus non-black race/ethnicity in a subgroup analysis of a recent study of Medicare beneficiaries (34). However, unlike the earlier study (49), this study was not powered to study the sex-race interactions in early and late hip fracture mortality risks.

Type of fracture

Seemingly an unmodifiable risk factor, the type of hip fracture and consequently the type of surgical intervention result in differential survival (50). Intertrochanteric compared to femoral neck fractures led to significantly higher mortality risk at hospital discharge, at 1 year [relative risk (RR) 2.5; 95% confidence interval (CI) 1.3 - 5.1] (51), and up to10 years (RR 1.4; 95% CI 1.0-1.8) (29). The higher mortality rates with intertrochanteric fractures may be due to greater frailty before injury, older age, and more severe osteoporosis (52-55). This effect persisted after accounting for age and comorbid conditions; the functional outcomes among surviving patients was similar (51).

Perioperative factors and surgical complications

Postoperative complications of hip fractures such as infections and cardiovascular diseases are well-recognized causes of immediate mortality (32, 33, 35, 36, 56-58). Any major post-operative complication is associated with 90% increased mortality risk (32). Good surgical technique and minimization of operative delay (58-61) may minimize postoperative complications and improve early mortality outcomes, although studies are inconsistent (27, 62). In a meta-analysis, regional anesthesia appeared to reduce acute postoperative confusion but had no apparent effect on mortality (63). Appropriate perioperative management with antibiotics (64), blood transfusion (65), and prevention of deep venous thrombosis and pulmonary embolism (66, 67) also appear to improve mortality outcomes. In addition to these measures that reflect in-hospital quality of care, increase in hospital volume for hip fracture surgery has been associated with increased inmortality (27), although this finding is discordant with previous studies that either were small or did not adjust for confounding factors (68, 69).

Comorbidities and functional status

The severity of comorbidities, measured using the American Society of Anesthesiologists grading system, is an important predictor of mortality after a hip fracture (32, 40, 58, 70, 71). The more dependent the patient is in ambulatory status, activities of daily living (ADL), and instrumental ADL prior to hip fracture, the higher the mortality risk (32-34). Poor isometric knee extension strength may be a measure of frailty and old age but also has been shown to predict increased mortality independently after the fracture (72).

A substantially increased mortality risk after hip fracture was observed among subjects with more than 5 hospitalizations since availability of electronic inpatient records (26). Previous serious hospitalization as a surrogate for poor pre-fracture health did not increase the relative risk of demise. However, when calculated in absolute terms, previous serious hospitalization increased the attributable 5-year mortality risk from 9% to 26% (26). The relative attributable mortality risk of hip fracture was higher for women than men, increased with age, and was markedly lower when hazard ratios were adjusted for health status in another study (34). It is complex, however, to compare these figures due to the different methodologies and assumptions used in different studies.

Socioeconomic factors

In a large Danish case-control study, the excess mortality of hip fractures changed only slightly upon adjustment for pre-morbid conditions, except for income, suggesting the importance of socio-economic factors on better outcomes (35). Institutionalized patients suffer higher mortality after hip fracture (33, 73). Although elderly people with hip fractures reported living alone more frequently and were less likely to be health maintenance organization members, these and other socioeconomic factors had no association with on mortality in another study (34).

Osteoporosis interventions to reduce mortality

It remains unclear whether prevention of fractures using anti-osteoporotic therapies may extend life expectancy, and to what extent. In a recent randomized controlled trial of secondary fracture prevention (39), there was a 28% reduction of mortality after 16 months in the zoledronic acid group compared to the placebo group, in addition to prevention of recurrent symptomatic fractures. Mortality outcome was not one of the pre-specified study endpoints, and this unexpected finding has not been explained. Extremely large population cohort studies are needed to establish whether prevention of a secondary hip fracture will improve longevity. After a hip fracture has occurred, implementation of evidence-based clinical pathways appears to reduce postoperative morbidity, but may not affect mortality (74, 75). However, co-management of hip fracture patients by orthopedic surgeons and geriatricians may potentially improve outcomes (76, 77). In summary, reducing the number of hip fractures and optimizing immediate

post-fracture medical care may reduce mortality, particularly if the focus is on reducing comorbidities such as infection and cardiovascular complications immediately following this very serious yet common late-life event. Further studies are required to identify other factors in the process of care that are associated with better outcomes.

Vertebral fractures and mortality

Vertebral fractures are the most frequent complication of osteoporosis (14, 78). The lifetime risk of a clinically diagnosed vertebral fracture after the age of 50 is estimated to be 9% in men and 15% in women (79). However, only one-third of cases are clinically diagnosed and an even smaller proportion of patients are admitted to hospital (18, 80, 81). Compared to hip fractures, it is thus more even more challenging to analyze the mortality burden of vertebral fractures.

Many studies have indicated an increase in mortality risk after vertebral fracture (11-14, 16, 18, 20, 21, 23, 82, 83). Excess mortality varies substantially after a clinical vertebral fracture, with 1-year rates ranging considerably from 1.9 to 42% (Table III). Increased mortality risk appears lower than that for hip fractures (13), although one study, the Study of Osteoporotic Fractures, indicated higher mortality risk following vertebral fracture (RR = 8.6) compared to hip (RR = 6.7) (although the CIs overlapped) (12). As with hip fractures, mortality risk is most marked within the first year after fracture (12-14, 20, 82), but an increased mortality risk greater than that of the general population extends for up to 5-22 years (14, 82). In one of the longest cohort studies, with 22 years of post-fracture follow-up, the post-vertebral fracture survival curves of men and women were similar in general. The greatest divergence of survival curves from the age-expected norms occurred during the first 3 years in men (Fig. 2) but later (near the tenth year) in women (data not shown), compared to the general population. After the first decade, the curves converged towards expected mortality rates in both sexes. Despite this, mortality was significantly higher in those experiencing vertebral fractures than in the comparator group over the entire 22-year follow-up period (82).

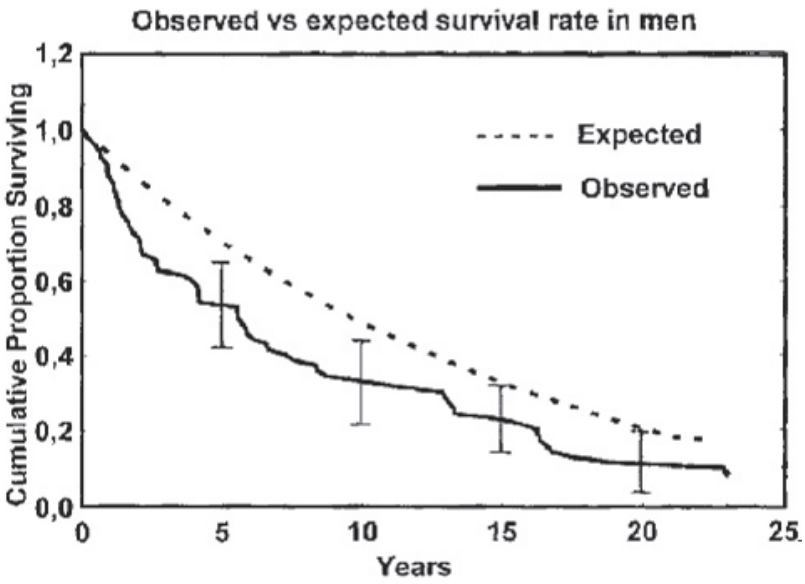

Fig. 2. Kaplan-Meier survival curve during a 22-year follow-up period after a clinically diagnosed vertebral fracture in men compared with the expected survival curve in the entire male Malmö population at risk. Ninety-five percent confidence intervals are shown at 5, 10, 15, and 20 years after the fracture event (82). *[Reprinted with permission from Hasserius R, Karlsson MK, Jonsson B, Redlund-Johnell I, Johnell O. Long-term morbidity and mortality after a clinically diagnosed vertebral fracture in the elderly--a 12- and 22-year follow-up of 257 patients. Calcif Tissue Int. 2005; 76(4): 235-42.]*

Mortality patterns with vertebral fractures

Although the absolute risk of mortality associated with vertebral fracture increases with age (11, 13, 20), the age-matched relative risk of death is higher in younger individuals and decreases with age (13, 20). In a study where low- and high-energy-related vertebral fracture were not distinguished, younger patients died more commonly from high trauma injuries or from secondary causes of osteoporosis (20). Similar to hip fracture studies, most (11, 13, 16) but not all vertebral fracture studies (20, 21) describe a higher mortality in men compared to women. Standardized mortality ratios (SMRs) were increased for incident and prevalent clinical vertebral fractures (13). Women with undiagnosed but severe vertebral fractures also had increased mortality risk in at least one study (18), contradicting the notion that subclinical fractures are less serious. The risk of death increased with number and severity of prevalent vertebral fractures (18, 22, 23).

Other risk factors for mortality with vertebral fractures

Similar to analyses of mortality after hip fractures, reduced survival is difficult to attribute directly to vertebral fracture, since mortality is also a result of underlying comorbidities and/or complications of prolonged hospital stays (84). Frailty and health-behaviors as well as the extent of comorbidities explain a significant proportion of the excess mortality risk (11, 15, 16, 18, 22) (Table IV). In a study based on hospital discharge ICD-9 codes, 26% of in hospital deaths was attributable to the fracture itself since this subgroup of patients had no identifiable comorbidity (11). In another study of nationwide hospitalizations for vertebral fractures in persons 50 years and older in Sweden, and based on assumptions that mortality in the first year was attributable to vertebral fracture, up to 28% of all deaths were attributed to vertebral fractures (20).

Prevalent versus incident vertebral fractures

Various studies have attempted to assess the mortality risk of prevalent versus incident *clinical* (11-14, 20) and *radiographic* vertebral fractures (16, 19, 82)

Table IV. Factors related to mortality following vertebral fracture (relative risk ratio (95% CI)).

Study:	Kado 1999 (18)	Kado 2003 (19)	Jalava 2003 (16)	Bouza 2007 (11)	Trone 2007 (22)
Sociodemographic and fall risk factors					
Men			3.0 (1.0–8.8)	1.5 (1.2–2.0)	1.8 (1.3–2.5)
Age	1.6 (1.5–1.6)	1.6 (1.5–1.7)		[a] 2.0 (1.3–2.8)	1.6 (1.5–1.7)
Vertebral fracture	1.2 (1–1.3)	I: 1.1(0.9–1.3) P: 1.2(1.0–1.3)	2.4 (0.9–6.2)		1.1 (0.8, 1.4)
Body mass index	0.9 (0.9–1)				
Total body fat					0.8 (0.8–0.9)
% Weight change		0.8 (0.8–0.9)			
Current smoking	2.0 (1.8–2.3)	1.3 (1.2–1.4)			1.6 (1.1–2.3)
Comorbidities					
Diabetes mellitus	1.8 (1.8–2.1)	1.9 (1.6–2.3)			
Hypertension	1.4 (1.2–1.5)				
Health status	1.6 (1.5–1.9)	0.7 (0.6–0.8)			
Serum ESR			1.0 (1.0–1.1)		
Alcohol			0.6 (0.3–1.2)		1.0 (0.9–1.0)
Pulse > 80/min		1.3 (1.1–1.5)			
Charlson Index 0					
1–2				2.1 (1.5–3.0)	
3–4				5.0 (3.0–8.1)	
>4				8.5 (5.1–14.1)	
Physical Function					
Physical activity	0.9 (0.8–0.9)	1.0 (0.9–1.0)			0.6 (0.5–0.8)
Inability to rise from chair		1.5 (1.3–1.7)			
Difficulty standing on feet for 2 hours		1.1 (1.0–1.2)			

95% CI: 95% Confidence Interval; I: incident vertebral fracture; P: prevalent vertebral fracture; a: age>80; ESR: erythrocyte sedimentation rate.

(Table III). Prevalent vertebral fractures differ from incident spine fractures in that they may have occurred many years prior to study entry and have a different prognosis for mortality. After adjusting for age, poor health, and other known predictors, including sex, body mass index, calcium, estrogen or thiazide use, thyroid medication, alcohol intake, exercise, current smoking, physical function, etc., prevalent vertebral fractures were an independent risk factor for mortality in some (18, 19, 22, 23), but not all studies (15, 16). One study found that women with two or more prevalent fractures had increased risk of all-cause mortality which was not seen in women with a single prevalent radiographic vertebral fracture (22). The authors indicated that a single vertebral fracture detected by quantitative vertebral height and area assessment (radiographic vertebral morphometry) cannot always distinguish between a congenital anomaly and a fracture, but two or more morphometric fractures are more likely to be osteoporotic fractures (22).Mortality risk appears higher in people with incident morphometric vertebral fractures compared to those who do not have incident vertebral fractures (19). However, after adjustment for 12 covariates, including age, low bone density, prevalent vertebral fractures, weight loss, inability to rise from a chair, and difficulty standing for more than 2 hours, the association between incident vertebral fractures and mortality was not significant. This finding suggests that incident vertebral fractures do not directly cause death. Women who had experienced both a prevalent and incident vertebral fracture had the highest mortality, but there was no significant interaction between prevalent and incident vertebral fracture status. In other words, stratifying by prevalent vertebral fracture status did not affect the multivariable results. While it is possible that frailty can be both a cause and effect of vertebral fractures, the authors suggested that vertebral fractures, physical function decline, and weight loss may all be proxy markers of an accelerated aging process rather than independent contributors to mortality (19).

Proximate causes of death after vertebral fracture

In the Study of Osteoporotic Fractures (18), women with severe vertebral deformities had an increased risk of death due to pulmonary causes such as chronic obstructive pulmonary disease and pneumonia, even after adjusting for long term glucocorticoid and tobacco use. Severe kyphosis is strongly associated with pulmonary deaths, possibly due to restrictive lung disease and reduced respiratory reserves. Several studies report a greater rate of cancer mortality in women with vertebral fractures compared to those without fractures (14, 18), even after excluding the possibility

of metastatic disease to the spine (18). In the Malmö population with vertebral fractures, cancer was significantly increased compared with the female, age-matched population at risk (82). In another study, however, there was no increased mortality risk in people with a history of vertebral fractures compared to the other patients (22), although the cause of death was unknown in 26% of the deceased. Differential classification of causes of death and the overall small number of deaths complicate meaningful comparisons across studies.

In summary, increased mortality rates have been observed after vertebral fractures, although the independent effect of the fracture on this outcome compared to the effect of comorbidities remains somewhat controversial. If a direct independent association between vertebral fracture and mortality exists, the pathophysiology of how vertebral fractures may lead to increased mortality remains unknown. While vertebral fractures may account partly for excess mortality, the underlying comorbidities and poor health status influence considerably the risk for vertebral fractures. This may be due either directly to the pathogenesis or by selection bias through increased medical surveillance of a sicker population with a higher risk of mortality. Beyond preventing future morbidity, it appears logical to manage post-vertebral fracture patients aggressively to potentially reduce the risk of death.

Conclusion

Hip and vertebral fragility fractures are associated with significantly increased mortality rates. No single factor predicts excess risk of death, and no proven solution to improving fracture survival in osteoporosis in all populations has been identified. The independent role of fractures versus other confounding factors, including functional status, comorbidities, capacity for independent living, etc., in increased mortality rates is uncertain. Aggressive treatment of osteoporosis, especially in patients who have already suffered from a fracture event, reduces morbidity and may translate into longer-term survival. Future research should help to better characterize critical predictors of mortality and to design cost-effective interventions with the goal to reduce short- and long-term morbidity and mortality in patients at greatest risk.

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