Determinants of mortality risk following osteoporotic fractures

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Purpose of review
Increased mortality risk is accepted for hip and vertebral fracture. Recent data suggest that other fracture types have also been linked to excess mortality. This article reviews the existing evidence on the pattern and determinants of postfracture mortality.

Recent findings
The pattern of mortality over time following hip and vertebral fractures has recently been clarified. Nonhip nonvertebral fractures at major, and even minor sites in older individuals have also been associated with excess mortality. Studies have revealed the higher excess mortality in men and in younger age groups for all fracture types. Despite the increasing knowledge on the fracture-mortality association, little is known about its cause. The role of co-morbidities is inconsistent across studies. Recent findings suggest low bone mass, bone loss and muscle weakness are linked to both fracture and mortality risk, and thus may play a role in postfracture mortality.

Summary
Nonhip nonvertebral fractures have recently been associated with mortality risk. Larger studies are needed to better understand which specific fractures and factors contribute to fracture-associated mortality risk. The role of bone loss in postfracture mortality needs to be validated in more studies, because of its potential reversibility with antifracture therapies.

Keywords
fracture, mortality, risk factors

INTRODUCTION

Osteoporosis is a common and increasing health problem globally. Its burden is due primarily to osteoporotic fracture, with direct annual costs of over $1.9 billion. Aside from the economic burden, osteoporotic fractures are associated with increased disability, risk of further fracture and more importantly and often ignored, premature mortality. The high mortality following hip and clinical vertebral fracture is well recognized and consistently reported. Mortality risk following other types of fracture is far less well studied. There is however, increasing evidence that major fractures [1,2], particularly humerus [3–5], pelvic [4], distal femur [4,6▪▪] and rib [4] fractures are also associated with excess postfracture mortality.

The cause of the high mortality risk following osteoporotic fracture is complex and not fully understood. For hip fracture, parameters related to surgery may account for some of the early mortality risk [7,8▪▪,9▪]. However, other types of fracture are less well studied and the direct causal link with mortality is hard to understand. The role of co-morbidities and prefracture status on postfracture mortality risk are the most commonly studied factors, but findings are not consistent across studies. On the other hand, fracture risk factors such as low bone mineral density (BMD), bone loss, muscle strength and function, have been linked to mortality risk in the general population, and recently documented to play a role in postfracture mortality. Similarly, the role of subsequent fracture on mortality risk has also been recently found to be significant.

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KEY POINTS

- Mortality risk is increased for hip, clinical vertebral and major fractures (such as humerus, ribs, pelvis, distal femur). Larger studies are needed to understand the role of individual fracture types, particularly the more distal sites on mortality risk.
- Men have greater excess postfracture mortality than women.
- Mortality risk is not constant over time. Excess mortality is highest immediately postfracture, but may stay elevated beyond 5 years. Subsequent fracture is also associated with increased risk, and may play a role in the long-term excess mortality.
- Fracture risk factors such as low bone mass, bone loss, muscle weakness and sarcopenia have been consistently linked to all-cause mortality and postfracture mortality.
- The severity and number of co-morbidities may also be determinants of postfracture mortality but findings are not consistent across studies.

This review summarizes recent evidence on the magnitude of the fracture-mortality association and highlights some of the most important research findings on the role of co-morbidities and fracture risk factors on the pattern of mortality risk following different types of fracture.

MAGNITUDE AND DETERMINANTS OF FRACTURE-MORTALITY ASSOCIATION

Mortality risk associated with osteoporotic fractures ranges from 15% to over two-fold above the mortality expected in general population [1,5,10]. The variation in the magnitude of postfracture mortality depends predominantly on the fracture type, age, gender and length of the study.

Role of fracture site

Hip fractures

Hip fractures are associated with the highest mortality rates among all osteoporotic fractures in all epidemiological studies [1,11] except one [4]. The magnitude of hip fracture mortality depends on the length of study, follow-up and age. Up to 30% of individuals with hip fracture are estimated to die in the first 2 years post fracture [9▪,12]. This equates to an excess mortality of over two-fold the expected general population mortality [13,14]. The yearly excess mortality from 22 cohorts in women and 17 in men was recently estimated in a meta-analysis [14]. Using a life table approach, investigators estimated an annual posthip fracture excess mortality of 8, 11, 18 and 22% at 1, 2, 5 and 10 years for women with hip fracture at age 80 compared with women without fracture. In men, the estimated annual posthip fracture excess mortality was even higher: 18, 22, 26 and 20% for 80-year-old men with hip fracture compared with those without fracture.

Although hip fracture occurs predominantly in the older groups, younger individuals have higher excess mortality compared with their nonfractured peers than older individuals. For example, in the Dubbo Osteoporosis Epidemiology Study (DOES), younger women with hip fracture had over eight-fold increased mortality risk compared with two-fold for those older than 75 [1]. Similar data on higher excess mortality in younger women with hip fracture vs. older has also been reported in a recent study from the Study of Osteoporotic Fractures [15]. In this study, age was inversely correlated with excess mortality. Women in the youngest age-group (60–69) had a five-fold mortality risk, whereas those 80+ did not have excess mortality. The reason behind the higher excess mortality following hip fracture in younger vs. older individuals is not known. One reason could be that younger participants would be expected to have much lower mortality rates compared with older participants and thus the excess mortality discrepancy reflects the general population life expectancy gap. It is also possible that individuals who experience hip fracture at a younger age have a poor health status [16], that could affect their survival. More studies are needed in order to understand the epidemiology of hip fracture in younger participants.

Vertebral fractures

Vertebral fractures are the most common type of osteoporotic fracture, representing one-third of all osteoporotic fractures [17], and are associated with significant morbidity and mortality [18,19]. However despite their severity, there are far fewer data on their mortality compared with that of hip fracture. Nevertheless, the majority [1,4,11,12,16–18,20], although not all [5] studies [1,4,20–22] that investigated outcomes following vertebral fractures reported increased mortality risk.

Their research poses a significant challenge due to the fact that about 30% of them are symptomatic or admitted to the hospital [23,24]. Symptomatic vertebral fractures are associated with increased risk of mortality in both women and men, with a magnitude ranging from 32% to over 13-fold above expected general population mortality [11,18,19].

Similarly to hip fracture mortality, age plays a role in the fracture mortality magnitude. In the DOES cohort, individuals who experienced a symptomatic vertebral fracture below 75 years of age had significantly higher excess mortality compared with those who had their first vertebral fracture after 75 years for both women [age-adjusted standardized mortality ratio (SMR) 3.77 (2.45–5.81) and 1.45 (1.14–1.84)] and men [age-adjusted SMR 4.19 (2.42–7.27) and 1.88 (1.37–2.59)] [1].

The effect of asymptomatic vertebral fractures on mortality risk is less well studied. The presence of multiple vertebral deformities was found to be associated with increased mortality risk in several studies [25–27]. However, the role of a single vertebral fracture on mortality is less clear with contradictory findings [25,27], and any effect may be mediated through increasing risk of new clinical vertebral fracture. In a study [28] from the DOES cohort, vertebral deformities were associated with high risk of incident vertebral fracture, which increased mortality risk.

Nonhip nonvertebral fractures

Nonhip nonvertebral fractures are the most common group of osteoporotic fractures, representing over half of all fractures occurring in the community. However, despite their frequency, there are very few studies on the adverse outcomes associated with them. Increased mortality risk associated with major nonhip nonvertebral fracture (a group of fractures including pelvis, distal femur, multiple ribs and humerus) was first demonstrated in DOES cohort over a 5-year follow-up [29]. Major fractures were associated with 2.0–2.2-fold increased mortality risk for both women and men, while minor fractures (forearm, wrist, metacarpal, ankle and metatarsal) were not associated with mortality risk. Subsequently, a long-term follow-up (> 18 years) from the same cohort, re-confirmed the excess mortality associated with major fracture, and also demonstrated increased mortality for minor fractures in the older (>75 years) individuals [1]. Notably, given that nonhip nonvertebral fractures represented half of all incident fractures in the cohort, they were responsible for over 40% of all deaths and contributed to a third of all excess mortality. Similarly high mortality risk associated with major fracture was reported by a hospital database study [30] from Maastricht. Several other studies [4,5,6▪▪,10,31] have reported increased mortality risk associated with individual fracture sites such as proximal humerus, ribs, pelvis, and distal femur. Proximal humerus has been consistently associated with high excess mortality ranging from 60% up to five-fold (REF), in both sexes, except one study [5], which reported long-term mortality risk only in men but not in women. Distal forearm fractures on the other hand, have been consistently reported to not be associated with increased mortality risk [4,5,31], except in one study [10], which reported increased mortality in men with wrist fracture.

Men have higher mortality risk than women

Epidemiological studies have consistently shown that men have higher re-fracture [32] and mortality risk [5,10,12,13,33▪] despite having a lower initial fracture risk.

In a recent Dutch study, male sex was an independent predictor of increased mortality risk following all fracture types, being associated with a 74% increased risk compared with women [adjusted hazard ratio (HR) 1.74 (1.44–2.10), $P < 0.0001$]. The magnitude of the sex discrepancy in mortality rates may be even higher for the most severe fractures such as hip and vertebral fracture. In the DOES cohort, the absolute mortality rates were higher for men than women for all types of osteoporotic fractures, but particularly for hip and vertebral fractures. Similar findings were reported in the Manitoba Canadian health database in which the highest mortality rates were observed in men, particularly for hip, vertebral and humerus fractures. Interestingly, in this study [10], the discrepancy between sex mortality was constant over time, and persisted beyond 5 years postfracture.

The differences in the survival between the sexes are not fully understood. It is possible that men who sustain fracture have a poorer health than women with fracture, and that could influence their survival. The sex difference in co-morbidity profiles in patients with hip fracture was reported in the Standardized Audit of Hip Fractures in Europe [8▪▪]. In this study males with hip fracture had more co-morbidities, and were more likely to develop pneumonia and cardiac complications compared with females with hip fracture. More epidemiological studies including all types of osteoporotic fractures are needed in order to better understand the sex differences in survival.

The role of time post initial fracture

Several long-term epidemiological prospective studies [1,2,4,10] have reported the pattern of postfracture mortality risk over time. Postfracture mortality is highest in the first 5 years postfracture and then declines towards the general population mortality rates except for hip fracture where the increased mortality lasts longer [1,2,4,10]. The pattern of mortality with time has been best described

for hip fractures. Data on excess posthip fracture mortality over time were examined in a recent meta-analysis. In all included studies, the magnitude of mortality risk was very high immediately post-fracture and then decreased afterwards, but did not reach the expected background mortality for up to 10 years for any given age. All-cause excess mortality ranged between five-fold and eight-fold at 3 months, then declined to 2.9–3.7 at 1 year and to 1.8–2.0 at 10 years post fracture [14]. A similar pattern of excess mortality over the time was found in a meta-analysis of 22 studies. In this review mortality rates ranged between 8.4 and 36% in the first year postfracture, which corresponded to up to two-fold above the expected population mortality [13].

A similar pattern of excess mortality immediate after the fracture has also been described for vertebral fracture in several studies [1,4,11,22]. The pattern of mortality risk following symptomatic vertebral fractures is similar to that following hip fracture with the highest mortality recorded in the first 5 years postfracture [1,21].

For other fracture types, there are far fewer data. In the DOES cohort, the risk of mortality was elevated for the first 5 years postfracture for all types of fracture, including minor fractures in those older than 75 years [1]. Beyond 5 years, mortality risk was elevated only for hip fracture, and beyond 10 years none of the fractures was associated with excess mortality.

ROLE OF SUBSEQUENT FRACTURE

The role of subsequent fracture on mortality risk was first evaluated in the DOES cohort by comparing the pattern of excess mortality over the time for those with one vs. more than one fracture [1]. A subsequent fracture that occurred in the first 5 years post initial fracture, increased that initial 5 year mortality risk up to two-fold for both women and men and was higher than the excess mortality solely attributed to the initial fracture. Notably, the second fracture resulted in an excess mortality that remained elevated beyond the first 5 years in both women and men [age-adjusted SMR: 1.41 (1.01–1.97) and 1.78 (0.96–3.31) for women and men, respectively] [1]. Interestingly, a subsequent study [34] from the same cohort, demonstrated that the majority of the excess mortality beyond 5 years postfracture was attributable to the subsequent fracture, while those who survived for 10 years without experiencing a second fracture were at low risk of having either another fracture or premature mortality. The role of subsequent fracture in mortality risk has also been reported in a Dutch study. In this study [12] a subsequent fracture was an independent predictor of mortality risk (1.65-fold) after adjusting for age, sex and fracture type.

The understanding of the role of subsequent fracture in mortality risk is particularly important given its high frequency following all types of fracture and its potential to be prevented by antifracture therapy.

Role of bone loss

Low femoral neck BMD is a well-known fracture risk factor, which has also been reported as a determinant of all-cause mortality risk in the general population [35–37]. A meta-analysis of 10 studies, estimated that low bone mass was associated with both total cardio-vascular (1.13-fold per standard deviation (SD) lower bone density) and total mortality risk (1.17 fold per SD lower bone density) [38].

The additive effect of low bone mass, bone loss, weight loss and weight fluctuation in all-cause mortality was reported in the Dubbo Study [36]. Low baseline femoral neck BMD was associated with an increased risk in all-cause mortality risk in women [HR per SD: 1.3 (95% CI, 1.0–1.7)] but not in men [HR per SD: 1.1 (95% CI, 0.9–1.2)], whereas bone loss predicted mortality risk in both sexes [women HR 1.8 (1.2–2.5) per 5% bone loss/year and men 1.6 (1.1–2.5) per 5% bone loss/year]. The combination of low bone mass, bone loss and weight fluctuation explained approximately 36% of all deaths in women and 22% in men. Consistently with this data, accelerated rates of bone loss have also been found to be associated with postfracture mortality [39▪▪]. In this study [39▪▪] women and men in the highest quartile of bone loss (−1.33%/year for women and −1.35%/year for men) had ∼44–77% higher mortality rates compared with those who did not lose bone, even after adjusting for age, baseline BMD and co-morbidities.

The mechanism of increased mortality with accelerated bone loss is complex and is not fully understood. Bone loss may be a marker of frailty and ageing, and may be induced by inflammatory factors such as interleukin-6 [40], which are also associated with reduced survival [41]. It is also hypothesized that the increased mortality in individuals with accelerated bone loss may be due to a release of lead from the bone, which subsequently may predispose to cardio-vascular diseases. One study [42] has demonstrated that significantly higher lead concentrations are found in whole blood after menopause, a state of high bone turnover and bone loss, compared with the concentrations before menopause while another study [43] reported increased cardio-vascular mortality

in women with high levels of blood lead concentrations. However a causal relationship between bone loss, lead and mortality has never been demonstrated.

Muscle strength

Poor muscle strength is another factor that has been independently associated with both fracture and mortality risk [44,45]. The role of sarcopenia, which is a combined measure of muscle mass and strength has been recently reported to play a role in fracture, frailty and mortality risk [46▪].

The role of poor muscle strength in postfracture rehabilitation and ultimately survival has predominantly been studied post hip fracture where it has been found to play a significant role [19]. It was also found to be an independent predictor for increased mortality following all osteoporotic fractures in the Lieto and DOES studies [1,5].

It remains unclear whether mortality risk is related to underlying risk factors for both the fracture and mortality, or whether the fracture event may directly increase mortality risk or whether it may be a combination of factors.

The role of co-morbidities

Co-morbidities have been hypothesized to play a major role in the cause of postfracture mortality risk. Indeed several studies have found a positive association between the severity of co-morbidities and mortality risk. In a large survey of Medicare beneficiaries, after adjustment for co-morbidities, mortality risk following hip fracture diminished significantly in the early postfracture period (first 6 months) and disappeared altogether in the later (over 6 months) postfracture follow-up. Due to this dramatic reduction in excess mortality with health status adjustment, the authors concluded that most of the early deaths and all the late deaths were not attributable to hip fracture. The severity of co-morbidities has also found to play a role in the mortality risk following hospitalized vertebral fracture in a large Spanish study [21]. However, not all studies have found that co-morbidities play a role in postfracture mortality. In the Study of Osteoporotic Fractures, co-morbidity adjustment did not affect the hazard ratio of mortality for any of the clinical fractures analysed [11]. Similar findings of no trend of excess mortality with the number of co-morbidities were reported in a nationwide database of hip fracture. In this hip fracture study [7] all excess mortality has been linked to either the fracture event *per se* or to complications surrounding the fracture event.

In the studies that have reported a positive effect of co-morbidities on postfracture mortality, specific types of co-morbidities have been linked particularly to hip and vertebral fractures. Cardiovascular, renal, pulmonary diseases and reduced cognitive function have been reported in several studies of hip fracture mortality to play a role in postfracture mortality either through delaying time to surgery or increasing postoperative complications which both increase mortality risk [47,48]. Individuals with vertebral fractures, and particularly those with multiple vertebral compression fractures may develop pulmonary diseases because of progressive kyphosis, which leads to thoracic cavity reduction and decreased pulmonary function [49]. The role of co-morbidities in mortality associated with nonhip nonvertebral fracture is less clear. In the DOES cohort the number of co-morbidities did not play a significant role in mortality following all types of osteoporotic fracture. Similarly, in the Manitoba Healthcare database study, co-morbidities played little role in the first year postfracture, but, having six or more co-morbidities was associated with mortality risk. Thus, the role of co-morbidities in fracture-associated mortality remains controversial because of the paucity of data and inconsistencies among findings.

CONCLUSION

There is no doubt that hip and clinical vertebral fractures are associated with high mortality risk. However, accumulating evidence suggests that major nonhip nonvertebral fractures are also associated with excess mortality, and because of their high prevalence, are responsible for a significant number of fracture deaths in the community. There is a clear need for more large prospective studies to assess the effect of individual types of nonhip nonvertebral fractures on mortality risk, in order to determine which type of fracture are associated with excess mortality risk.

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