Fracture Liaison Service: Impact on Subsequent Nonvertebral Fracture Incidence and Mortality

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Background: A fracture liaison service model of care is widely recommended and applied, but data on its effectiveness are scarce. Therefore, the risk of subsequent nonvertebral fractures and mortality within two years after a nonvertebral fracture was analyzed in patients who presented to a hospital with a fracture liaison service and a hospital without a fracture liaison service.

Methods: In 2005 to 2006, all consecutive patients with an age of fifty years or older presenting with a nonvertebral fracture were included. In the group that presented to a hospital without a fracture liaison service (the no-FLS group), only standard fracture care procedures were followed to address proper fracture-healing. In the group that presented to a hospital with a fracture liaison service (the FLS group), dual x-ray absorptiometry scans and laboratory testing were performed, and if applicable, patients were treated according to the Dutch guideline for osteoporosis. The risk for subsequent nonvertebral fracture and mortality were analyzed using multivariable Cox regression models with adjustments for age, sex, and baseline fracture location.

Results: In total, 1412 patients presented to the fracture liaison service (73.2% were women, and the mean age was 71.1 years), and 1910 underwent standard fracture care (69.8% were women, and the mean age was 69.5 years). After adjustment for age, sex, and baseline fracture location, patients who attended the fracture liaison service had a significantly lower mortality risk (hazard ratio: 0.65; 95% confidence interval [CI]: 0.53 to 0.79) over two years of follow-up. The subsequent nonvertebral fracture risk was also significantly lower in the patients in the FLS group, but this effect was time-dependent, with a hazard ratio of 0.84 (95% CI: 0.64 to 1.10) at twelve months and 0.44 (95% CI: 0.25 to 0.79) at twenty-four months.

Conclusions: Patients seen at the fracture liaison service had a significantly lower mortality and subsequently a lower risk of nonvertebral fracture than those not seen at the fracture liaison service, with a reduction of 35% and 56%, respectively, over two years of follow-up. A fracture liaison service appears to be a successful approach to reduce the number of subsequent fractures and premature mortality in this cohort of patients.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

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Patients with a fracture after the age of fifty years are at increased risk of sustaining a subsequent fracture, which is highest in the short-term (less than two-year) period after the initial fracture[1-8]. Fracture liaison services have been developed and implemented to identify, evaluate, and treat patients with a recent fracture[9], but they differ in the way that they identify, assess, and treat individuals at high risk of a subsequent fracture[10-12]. Patients with a recent fracture have not only an increased risk of subsequent fracture but also an increased risk of mortality, especially after hip and major fractures[13,14].

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TABLE I Baseline Characteristics of Patients Treated at a Hospital with a Fracture Liaison Service (FLS) and at a Hospital without a Fracture Liaison Service

Baseline Variable	FLS Group (N = 1412)	No-FLS Group (N = 1910)	Total (N = 3322)	P Value*
Women *(no. [%])*	1033 (73.2)	1334 (69.8)	2367 (71.3)	0.037
Age† *(yr)*	71.1 ± 11.8	68.3 ± 11.0	69.5 ± 11.4	<0.001
Baseline fracture location† *(no. [%])*				<0.001
Hip	280 (19.8)	303 (15.9)	583 (17.5)	
Major	298 (21.1)	357 (18.7)	655 (19.7)	
Minor	834 (59.1)	1250 (65.4)	2084 (62.7)	

*Chi-square tests and Student t tests were used. †The values are given as the mean and the standard deviation. ‡Major fractures were those of the pelvis, proximal part of the tibia or humerus, multiple ribs, and distal end of the femur, and minor fractures were all other fractures.

Recent studies have indicated that mortality could be reduced by bisphosphonate treatment, in addition to its role in fracture prevention. A 28% reduction in mortality was reported after zoledronic acid therapy in patients with a recent hip fracture and a life expectancy of more than six months[15]. A significant reduction in mortality of 11% was found in a recent meta-analysis of the effect of osteoporosis medication on mortality[16,17].

In a previous before-and-after impact study (1999 to 2001 versus 2004 to 2006), the two-year risk reduction of repeat nonvertebral fracture and mortality was 35% and 33%, respectively[18]. However, other components of postfracture care could have changed over time.

Therefore, the aim of the current study was to evaluate the impact of the fracture liaison service by comparing subsequent nonvertebral fracture risk and mortality between two hospitals within the same time frame, one with and one without a fracture liaison service, over a two-year follow-up period.

Materials and Methods

Study Design

This prospective study was conducted in two hospitals in the Netherlands: one university hospital with a fracture liaison service (the FLS group) and one general hospital without a fracture liaison service (the no-FLS group). In the fracture liaison service, a dedicated fracture nurse systematically evaluated all patients with an age of fifty years or older who were able and willing to participate, at the outpatient clinic after a recent nonvertebral fracture.

The fracture nurse checked whether all patients who were fifty years or older with a fracture had an appointment at the fracture liaison service using the emergency department computer system. If not, an invitation was sent by mail. All fracture patients were seen at the fracture outpatient clinic by an orthopaedic trauma surgeon. The evaluation consisted of a systematic evaluation of clinical risk factors (medical history, exposure to medication, and fall-related risk factors). The clinical and fall-related risk factors are published elsewhere[19]. Additionally, the Groningen Activity Restriction Scale (GARS) was used to estimate the disability in activities of daily living[10,12,20]. Bone mineral density measurement of the femoral neck and lumbar spine was assessed using a Hologic densitometer (QDR-4500 Elite; Hologic). All patients with a T-score of −2.5 standard deviations or less at either location were advised to start treatment according to the Dutch osteoporosis guideline[10,20]. The evaluation consisted of two appointments: in the first one, the fracture liaison service was explained, and informed consent was obtained; and in the second one, all risk factors and dual x-ray absorptiometry results were collected. On the basis of the results, the fracture nurse informed the patient and advised him or her to start treatment when indicated (antiosteoporotic medication and calcium and vitamin-D supplements).

In the no-FLS group, patients received standard fracture care concentrated on fracture-healing, not on the possible predisposing factors.

All consecutive patients with an age of fifty years or older who were living in the postal area of the hospitals with and without a fracture liaison service and who presented with a recent nonvertebral fracture in 2005 and 2006 were included in the study. Patients with pathological (non-osteoporosis-related) or vertebral fractures were excluded. Baseline and subsequent fractures were classified according to the International Classification of Diseases, Ninth Revision codes and were additionally categorized on the basis of the fracture location as hip, major (pelvis, proximal part of the tibia or humerus, multiple ribs, and distal end of the femur), or minor (all remaining fractures)[13]. These categories were chosen because hip and major fractures are associated with increased mortality[1,13]. Data on mortality were obtained and confirmed using the national obituary database. Date, but not cause, of death is registered in this database. According to the intention-to-treat principle, patients who were unable or not willing to visit the fracture liaison service were included in the FLS group and in all analyses.

Statistical Analysis

Characteristics between the FLS and no-FLS groups were analyzed with the Pearson chi-square test for dichotomous variables and independent-samples t test for continuous variables. The effect of the fracture liaison service on subsequent fracture and mortality was analyzed using multiple Cox proportional hazard models. For the death-censored analyses of subsequent fracture, follow-up time was set as the time between the first and subsequent fracture, death, or end of the two-year follow-up period. For the analysis with death as the event, the follow-up interval was set as the time between the first fracture and death or the end of the two-year study period.

The proportional hazard assumption was checked using Schoenfeld residuals. If this assumption was violated, i.e., the hazard ratio was not constant over time, time-dependent Cox proportional hazard models were used. Subgroup analyses, i.e., multiple Cox proportional hazard regressions, were performed for baseline fracture location and in a subgroup analysis comparing the no-FLS with the FLS group (divided into "shows" and "no-shows"). All analyses were performed with adjustments for sex, age, and baseline fracture location, except the subgroup analyses in which adjustments were made for sex and age. All statistical analyses were performed using SPSS for Windows software (version 18.0; SPSS, Chicago, Illinois). MATLAB (version 7.10; MathWorks, Natick, Massachusetts) was used to plot the subsequent fracture rate for patients with a baseline hip fracture and for those with a baseline minor fracture.

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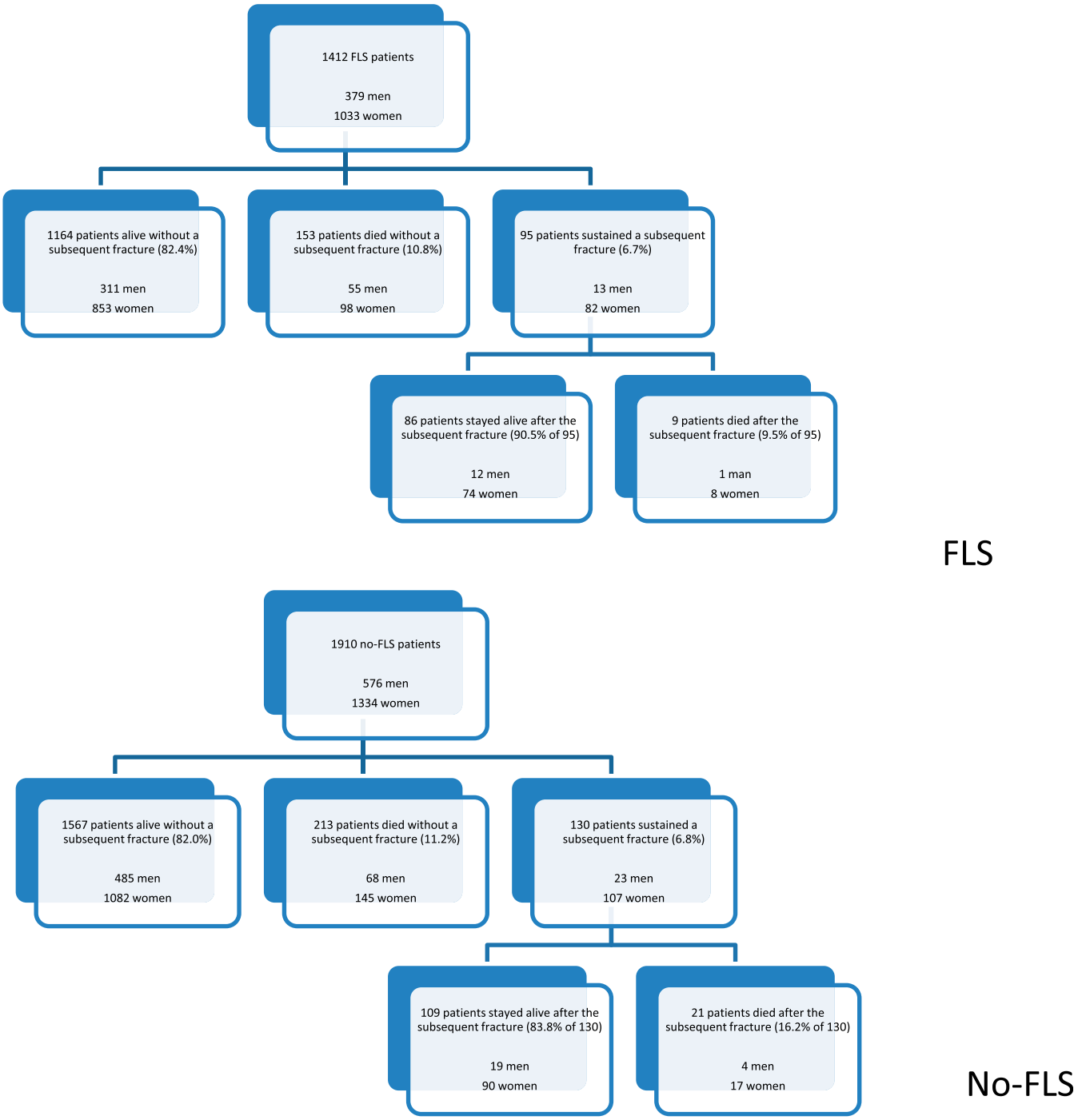

Fig. 1

Flowchart of patient categories over a two-year follow-up period for the university hospital with a fracture liaison service (FLS) and at the general hospital without a fracture liaison service (no-FLS).

Results

Patient Characteristics

In total, there were 3322 patients (1412 in the FLS group and 1910 in the no-FLS group), of whom 71.3% were women (Fig. 1). Differences in patient characteristics between the FLS group and the no-FLS group are shown in Table I. Of the 1412 patients in the FLS group, 67.8% participated in the fracture liaison service (the "shows"). Within the FLS group, the "no shows" (patients not willing or not able to participate) were significantly older (76.9 years versus 68.3 years; $p < 0.001$) and

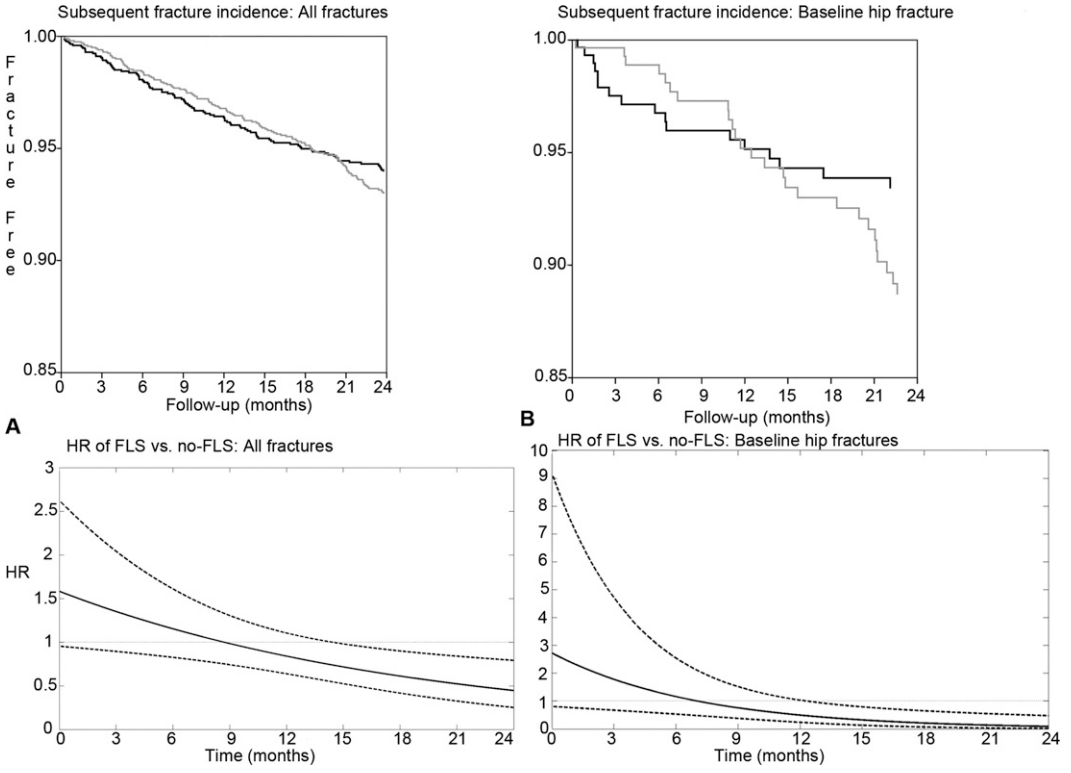

Fig. 2

Figs. 2-A and 2-B Subsequent fracture incidence. **Fig. 2-A** Cumulative survival rate with subsequent fractures as the event for the patients included at the hospital with a fracture liaison service (the FLS group; black line) and at the hospital without such service (the no-FLS group; gray line). Subsequent fracture incidence for all fractures (top). Hazard ratio (continuous black line) and 95% confidence interval (95% CI; black dashed lines) for subsequent fractures as the event comparing patients included in the FLS group and the no-FLS group (bottom). After fifteen months, the subsequent fracture hazard ratio (HR: 0.72, 95% CI: 0.52 to 0.98) was significantly lower in the FLS group. **Fig. 2-B** Cumulative survival rate with subsequent fractures as the event for the patients in the FLS group (black line) and in the no-FLS group (gray line). Subsequent fracture incidence for baseline hip fractures (top). Hazard ratios (continuous black line) and 95% CI (black dashed lines) for subsequent fractures as the event for the subgroup with a baseline hip fracture comparing patients in the FLS group and the no-FLS group (bottom). After thirteen months, the subsequent fracture hazard ratio (HR: 0.43, 95% CI: 0.20 to 0.94) was significantly lower in the FLS group.

had sustained more hip fractures (34.1% versus 13.1%; $p < 0.001$) than the "shows."

Subsequent Nonvertebral Fractures

In total, 225 patients (6.8%) sustained a subsequent nonvertebral fracture within two years after their baseline nonvertebral fracture: 130 patients (6.8%) in the no-FLS group and ninety-five (6.7%) in the FLS group (Fig. 1). After adjusting for sex, age, and baseline fracture location, the general Cox proportional hazards model showed no significant difference in subsequent fracture risk between the FLS and no-FLS groups (hazard ratio: 0.88; 95% confidence interval [95% CI]: 0.67 to 1.14) (Table II, Fig. 2-A).

However, since the assumption of proportional hazard was violated for the FLS versus the no-FLS group, the time-dependent Cox model should be applied instead of the general Cox model. No significantly lower subsequent fracture risk was detected in the FLS group compared with the no-FLS group after six months and twelve months of follow-up; however, a lower risk was found from fifteen months onward (hazard ratio at fifteen months: 0.72; 95% CI: 0.52 to 0.98; Table II, Fig. 2-B).

The subgroup analyses according to baseline fracture location showed no significant difference in subsequent nonvertebral fracture risk between the FLS and no-FLS groups (Table II).

However, for the hip fracture subgroup, the proportional hazard assumption was violated. The results of the time-dependent Cox model showed no significant differences between the FLS and no-FLS groups at six months and twelve months of follow-up. However, from thirteen months onward, the risk was significantly lower in the FLS group (hazard ratio: 0.43; 95% CI: 0.20 to 0.94), and remained lower during follow-up (Table II).

A subgroup analysis comparing the no-FLS with the FLS group (divided into "shows" and "no-shows") demonstrated no overall significant difference with regard to subsequent fracture incidence ($p = 0.085$).

TABLE II Multivariable Cox Regression Analysis on Subsequent Fracture Incidence and Mortality Between the Groups Treated at a Hospital with a Fracture Liaison Service (FLS) and a Hospital without a Fracture Liaison Service

		Multivariable with the Time-Dependent Cox Model†			
	Multivariable*	Time Dependency	6 mo	12 mo	18 mo	24 mo
Fracture risk						
FLS vs no-FLS‡	0.88 (0.67-1.14)	Yes	1.15 (0.85 – 1.60)	0.84 (0.64 – 1.10)	0.61 (0.42 – 0.90)	0.44 (0.25 – 0.79)
Baseline hip fracture§	0.63 (0.34-1.18)	Yes	1.16 (0.53 – 2.55)	0.50 (0.24 – 1.04)	0.21 (0.07 – 0.65)	0.09 (0.02 – 0.48)
Baseline major fracture	0.89 (0.51-1.56)	No				
Baseline minor fracture	0.98 (0.69-1.34)	No				
Mortality risk						
FLS vs. no FLS	0.65 (0.53-0.79)	No				
Baseline hip fracture	0.67 (0.49-0.91)	No				
Baseline major fracture	0.57 (0.37-0.89)	No				
Baseline minor fracture	0.74 (0.51-1.07)	No				

*The values are given as the hazard ratio (HR), with the 95% confidence interval (95% CI) in parentheses, after adjusting for sex, age, and baseline fracture location. †The values are given as the hazard ratio, with the 95% CI in parentheses. ‡The difference was significant at fifteen months (HR, 0.72; 95% CI, 0.52 to 0.98) (see also Figs. 2-A and 2-B). §The difference was significant at thirteen months (HR, 0.43; 95% CI, 0.20 to 0.94) (see also Figs. 2-A and 2-B).

Mortality

In total, 396 patients (11.9%), including 162 (11.5%) in the FLS group and 234 (12.3%) in the no-FLS group, died within two years (Fig. 1).

The proportional hazard assumption was not violated for mortality. Mortality risk was significantly lower in the FLS group than in the no-FLS group (Table II, Fig. 3-A). Significant interaction was found between treatment at the fracture liaison service and sex. Separate analyses for sex showed that women in the FLS group had a significantly lower mortality risk (hazard ratio: 0.57; 95% CI: 0.44 to 0.73). In men, the difference was not significant (hazard ratio: 0.81; 95% CI: 0.57 to 1.16).

The subgroup analyses according to baseline fracture location showed that mortality risk was significantly lower in the FLS group after baseline hip fracture and after baseline major fracture, with a similar but not significant trend after baseline minor fracture (Table II, Figs. 3-B and 3-C). Again, the proportional hazard assumption was not violated. A subgroup analysis comparing the FLS group (divided into "shows" and "no-shows") and the no-FLS group indicated that the mortality

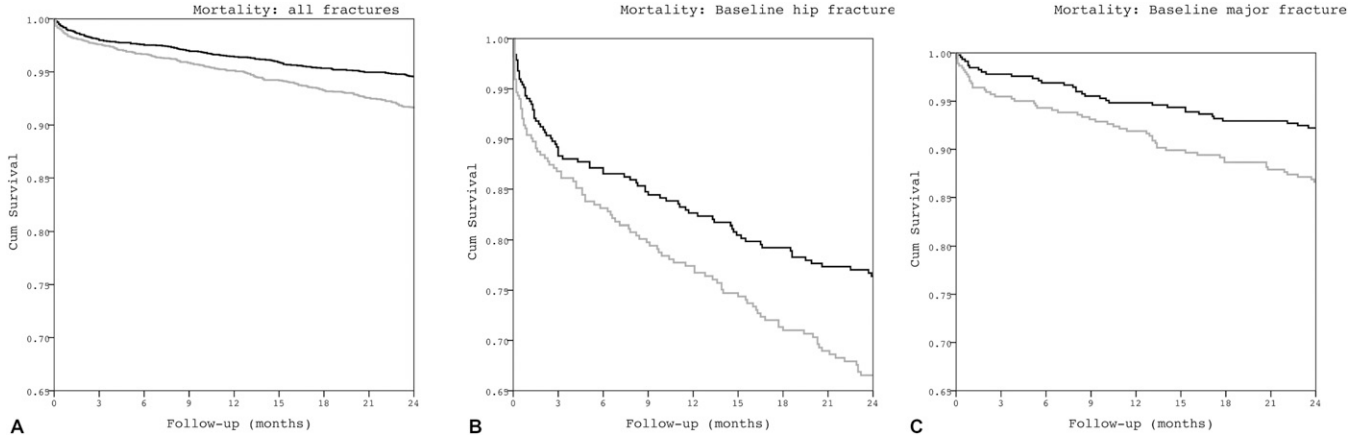

Fig. 3

Mortality incidence. Cumulative survival rate with mortality as the event for the patients in the FLS group (black line) and the no-FLS group (gray line). **Fig. 3-A** All fractures. **Fig. 3-B** Baseline hip fractures. **Fig. 3-C** Baseline major fractures.

rate was significantly lower in the patients who attended the fracture liaison service (the "shows") compared with the no-shows in the FLS group (hazard ratio: 0.42; 95% CI: 0.30 to 0.60) and the no-FLS group (hazard ratio: 0.40; 95% CI: 0.29 to 0.54). This effect was mainly driven by baseline hip fracture (a hazard ratio of 2.80 [95% CI: 2.18-3.58] for hip fracture compared with minor fracture and 1.64 [95% CI: 1.27 to 2.13] for hip fracture compared with major fracture).

Discussion

In this study, patients with a nonvertebral fracture who presented to a hospital with a fracture liaison service and those seen at a hospital without a fracture liaison service were compared with regard to the subsequent fracture incidence and mortality rate over two years of follow-up. There was a significant time-related lower incidence of subsequent nonvertebral fracture after correction for age, sex, and baseline fracture location in patients evaluated and treated, according to the Dutch guideline on osteoporosis published in 2002, in the FLS group compared with the no-FLS group. No significant difference in fracture rate was found during the first year; however, from the second year on, the fracture incidence was 28% lower at fifteen months and 56% lower at two years. These data are consistent with our previous results that showed an overall lower subsequent nonvertebral fracture incidence of 35% after the introduction of a fracture liaison service compared with five years earlier without a fracture liaison service[18]. Subgroup analysis according to baseline fracture indicated that the time-dependent effect on subsequent nonvertebral fractures was mainly driven by the effect in patients with a baseline hip fracture, since the subsequent incidence of nonvertebral fracture was 57% to 91% lower after a hip fracture in the FLS group, without differences after baseline major or minor nonvertebral fractures.

Mortality rate was 35% lower in the FLS group than in the no-FLS group after correction for age, sex, and baseline fracture location. The difference in mortality was not time-dependent. On the basis of subgroup analysis according to baseline fracture location, significant differences were found after baseline hip (−33%) and major fractures (−43%), but not after minor fractures.

Remarkably, fewer patients died in the FLS group; therefore, more patients survived to be at risk for a subsequent fracture, but still there was a significant reduction of subsequent nonvertebral fractures in the second year of follow-up. Also, despite the fact that patients in the no-show FLS group were older, had more hip fractures at baseline, and had more risk factors for subsequent fractures and mortality, we found a lower incidence in mortality and subsequent fractures (in the second year) for the total FLS group compared with the no-FLS group. Previous studies have shown similar results with regard to subsequent fracture risk and mortality[1,2,5,13,14]. A recent study showed that, in patients with an age of sixty years or older, the relative risk in subsequent fracture incidence was 1.95 for women and 3.45 for men[1]. Two retrospective studies showed an absolute risk of subsequent fractures of 10.8% in a two-year follow-up period and 17.6% in a five-year follow-up period of all fracture patients with an age of more than fifty years[2,5]. Fractures increased the risk of mortality, especially after a hip fracture[13]. Another study showed an increased mortality risk after all types of fragility fractures, which was highest within the first five years of follow-up[14]. However, in none of those studies was the outcome for patients treated in a hospital with a fracture liaison service compared with that for patients treated in a hospital without such a service. The findings in the present study strongly support the concept that a fracture liaison service can reduce both fractures and mortality[21].

Many randomized controlled trials have included patients with a prevalent vertebral fracture of unknown date with and without bone mineral density criterion. In those studies, there is a reduction of subsequent hip, nonvertebral fracture, and vertebral fracture, depending on treatment.

Only one randomized controlled trial has demonstrated a mortality reduction after treatment with a yearly administration of the intravenous bisphosphonate, zoledronic acid, in patients with a recent hip fracture compared with those receiving a placebo[15]. That study included a subgroup of patients with a recent hip fracture who had, according to the investigator, a life expectancy of more than six months and had no bone mineral density restrictions. It was, to our knowledge, the first randomized controlled trial in which an effect on mortality was demonstrated. Mortality decreased from sixteen months on when the first zoledronic acid infusion was given from four to six weeks after the hip fracture. In contrast, we found a lower mortality rate that was independent of time.

Several studies have found that antiosteoporotic treatment not only decreased the fracture rate and increased the quality of life, but also decreased mortality. In a meta-analysis of randomized controlled trials of bisphosphonates, mortality was 11% lower for the treatment groups than for the placebo groups[16]. Patients with a hip fracture who used oral bisphosphonates showed a 27% reduction in mortality compared with those who did not use them[22]. In a three-year prospective study of 220 patients with a recent hip fracture, mortality was 60% lower in each year for patients with a T-score of less than –1.5 who received bisphosphonates[23]. In a prospective cohort study, treatment with bisphosphonates was associated with a 69% reduction in mortality rate during longitudinal follow-up[17].

The mechanisms by which mortality is reduced are still unclear and seem to be multifactorial. They may be related to extraskeletal effects of bisphosphonates[17] or calcium and vitamin D or other unclear mechanisms. One explanation could be the prevention of (subsequent) fractures. In our previous research, patients with a subsequent fracture had a higher risk of mortality after the subsequent fracture compared with patients without a subsequent fracture[14,18]. However, fracture prevention seems to have only a small effect on mortality reduction. In the randomized controlled trial of intravenous bisphosphonate, 8% of the overall 28% mortality reduction could be attributed to fracture risk reduction[24]. Vitamin-D insufficiency is associated with osteoporosis and seems to be associated with other medical conditions. A recent study evaluated antiosteoporotic treatment in hip fracture patients in a nationwide database and

found an association between the use of antiosteoporotic treatment and vitamin D and calcium supplements and reduced mortality after hip fracture of 38% in women[25]. In men, this reduction was 26% and was seen only after the use of vitamin D and/or calcium supplements[25]. Another positive effect on the patient's overall health, thereby reducing mortality, might be the attention of the fracture nurse to the fracture patient and his or her overall medical problems. Unfortunately, we had data only on subsequent fractures, mortality, sex, age, and fracture location, and therefore we could not measure this possible positive effect.

The lower mortality in the FLS group in our study can only be partly explained by treatment with bisphosphonates and calcium and vitamin D, since only a limited number of patients were on bisphosphonate therapy, which was given to the participating patients who had bone mineral density-defined osteoporosis (approximately 50%). We did not have data about the percentage of patients treated with antiosteoporotic medication in the no-FLS group, but postfracture treatment and persistence of treatment at the time of this study was known to be low[26].

A strength of our study is that all consecutive patients who presented with a nonvertebral fracture in both hospitals were included in the analysis according to the intention-to-treat principle. The lower fracture and mortality rates were found in the total FLS group, despite the inclusion of no-show patients who were significantly older and had more baseline hip fractures. A limitation of this study is that it was not a randomized controlled trial. Therefore, other possible confounders could not be ruled out, especially since we did not have additional information about management in the no-FLS group. Also, baseline differences between the groups with regard to sex, age, and baseline fracture location were a limitation of this study; however, we adjusted the Cox regression analyses for these known factors. Cox regression analyses adjusted for age, sex, and baseline fracture location showed a time-dependent effect (Figs. 2-A and 2-B), whereas the absolute risks of a subsequent fracture were comparable (6.7% in the FLS group and 6.8% in the no-FLS group). The difference in the conclusions is due to the fact that there is a time-dependent factor, which is not taken into account in an absolute risk analysis. More specifically, the effect of the fracture liaison service is more pronounced after one year than during the early months. This is probably due to the effect of bone-directed therapies (calcium, vitamin D, and bisphosphonates) and therapies directed at secondary osteoporosis and metabolic bone diseases. The intervention continued after the visit at the fracture liaison service and was not the standard of fracture care in the hospital without such a service.

In the Netherlands, bone mineral density measurements and outpatient clinic visits are always covered by health insurance. However, travel costs and parking charges are not reimbursed. Recent cost-effectiveness analyses showed that fracture liaison services are cost-effective in the treatment of patients with a fragility fracture for the prevention of additional fractures[27,28]. The American Society for Bone and Mineral Research Task Force recently had an article published about making the first fracture the last[29]. The authors concluded that the fracture liaison service was the most important tool for such a change in fracture patients and that implementation would still be challenging in some ways[29].

In conclusion, patients with a recent nonvertebral fracture who were evaluated at the hospital with a fracture liaison service had a significantly lower mortality than did patients in a hospital without a fracture liaison service. Subsequent fracture risk was significantly lower after fifteen months and decreased by up to 56% after two years of follow-up for the patients evaluated at the hospital with the fracture liaison service. These results indicate that a fracture liaison service should be considered for patients within the studied age group with a recent fracture, especially after a recent hip or other major fracture. ■

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